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Manuscripts of three types of original work are desired for publication:

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THE TWELFTH ANNUAL MEETING

The Twelfth Annual Meeting of the Association for the Study of Internal Secretions will be held at Minneapolis, Tuesday, June 12, 1928. There will be a morning and an afternoon session, as has been the custom during the past years. The hours for these will be announced later.

The meeting will be held in the Loring Theater, which is located on 14th Street, just off of Nicollet Avenue, about two and one-half blocks from the Auditorium.

Those desiring hotel accommodations during the period of the American Medical meeting should take the matter up at an early date with Dr. F. G. Benn, 1114 Donaldson Building, Minneapolis, Minn., stating what accommodations you desire and the approximate price you wish to pay.

Our program is rapidly being completed. We have received the following information regarding the papers arranged for at the present time:

"The Relation of Infections to Goiter," Dr. W. H. Cole, Washington University, St. Louis.

"Iodine Deficiency Symptoms and Their Significance in Animal Nutrition and Pathology," Professor Evvard, Iowa State College of Agriculture and Mechanic Arts, Ames, Iowa.

"The Clinical Syndrome of Transitional Pituitary Adenomas," Drs. H. Cushing and Percival Bailey, Peter Bent Brigham Hospital, Boston.

"The Influence of the Anterior Hypophysis upon the Development and Activity of the Gonads as Indicated by its Experimental Ablation and Transplantation," Dr. Philip E. Smith, Columbia University, New York.

"The Relation of the Internal Secretions to Calcium Metabolism," Dr. Jos. C. Aub, Massachusetts General Hospital, Boston.

"The Relationship of Iodine to Thyroid Hyperplasia and Function," Dr. J. E. Else, Portland, Oregon.

"Exophthalmic Goiter and Adenomatous Goiter," H. S. Plummer, Mayo Clinic, Rochester, Minn.

"Hypophysectomized Puppies," F. L. Reichert, Stanford Hospital, San Francisco.

"The Normal Proportions of the Different Constituents of the Human Hypophysis," A. T. Rasmussen, University of Minnesota.

A paper is also being prepared by Dr. E. M. K. Geiling of Johns Hopkins University, but we do not have the title at this time.

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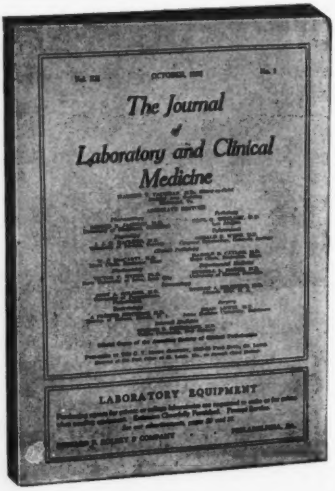

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Endocrinology

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STUDIES OF THE ENDOCRINE GLANDS. I. A GENERAL METHOD FOR THE DIAGNOSIS OF ABNORMAL FUNCTION

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This paper is the first of a series summarizing the results of a study on the diagnosis of endocrine diseases by objective methods. The work was begun in 1912 and in its course nearly 3,000 individuals have been carefully studied by a large group of clinicians and laboratory workers.

During the past few years several brief papers have appeared (1) presenting certain preliminary statements on the results of these studies. These have been supplemented by the reports of several clinical investigations based upon the method (2). With the completion of a series of 1,000 cases in which this procedure has been applied,* it has seemed desirable to present the facts thus far elicited with such conclusions as they may be felt to warrant. The present paper, as the title implies, deals with the general technique. Subsequent papers will present the details of the characteristic pictures of each of the

* Since beginning the compilation of the data here presented, over 2000 additional cases have been studied. The findings in the second group confirm and amplify, in a most gratifying manner, the conclusions drawn from the first.

several established endocrine entities. Finally, special treatment will be accorded those conditions which simulate endocrine disease and are frequently erroneously ascribed to it, but which can be shown by objective study to result from disease states not associated with the ductless glands.

The science of endocrinology, if so ambitious a designation be warranted, constitutes one of the newer chapters in medical history, and one that is still in the writing. True, the general concept of an internal secretory activity was first offered many centuries ago, but in this earlier form it derived solely from uncontrolled speculation and not from observation and experiment. First in the 19th century did certain definite, well-described clinical entities come into being in which an endocrine etiology was recognized by the individual authors whose names these syndromes bear, and toward the end of this period active glandular extracts were prepared and therapeutically applied. Finally, at the very beginning of the present century, Abel and others isolated the first active principle in a pure state.

These investigations, of which this paper is the first formal statement of results, are the expression of an effort to establish a series of objective criteria both for the general identification of disturbed endocrine function, and particularly for the determination of the individual gland involved. The field of so-called vital function testing has offered rich possibilities both by standardizing tests already described and by formulating new procedures when such were needed.

In the main, vital function tests have been designed to indicate an individual departure from the normal and have sought a marked degree of specificity. With the highly complex control of individual bodily functions, it has followed naturally that the reporting of each new test has been a signal for the recording of sweeping exceptions of both a positive and negative character. By questioning the specific character of the test its results have lost authority, and this in turn has frequently discouraged further study and application. Such an outcome is unfortunate and unwarranted. The level of any body function is certainly controlled by a large number of interrelated agencies which are mutually dependent and highly sensitive to changes in any one of them. The disturbance of any one equilibrium produces

changes in the balance of a number of other related control factors and may produce end results of a really significant character. As a vital function test can, at best, only record end results, a lack of complete specificity is confidently to be predicted. Even the highly differentiated tests in the field of serology fail to fulfill their purpose completely.

From another standpoint, however, this very multiplicity of control factors offers the largest element of value. The selection of a series of function tests gives not a single criterion of a single disturbed function, but a series of interrelated criteria in each of which several functional activities are involved. Thus while several factors influence the magnitude and direction of the result of each observation, it seems highly improbable that all of a series of widely divergent tests should be uniformly affected both in quality and amount by each of the several agents involved. The accuracy of this assumption has been amply verified in the series of cases reported in these papers. In passing, the writer wishes to state that no novelty is claimed for the majority of the tests, as such. It is chiefly in the angle of approach that the present method differs from others.

A point that cannot be over emphasized is the necessity for quantitative measurements. Differences as observed in many instances must be of degree and not of kind. Only the most exact methods available are suitable for this purpose and these should be as rigorously quantitative as possible.

The investigation has naturally divided itself into three phases. In the beginning, groups of apparently normal individuals were subjected to a long series of tests and observations under carefully controlled conditions, and the individual level of performance exactly recorded. Tests were retained or discarded as they served or failed to define standards of normality within reasonable limits of variation.

The second phase of the study called for the application of the same series of measurements to individuals in whom there existed clear-cut involvement of single glands. To this group belong male and female castrates and thyroid and pituitary patients after ablation operations. In addition, a few progessing cases of exophthalmic goiter and of acromegaly were studied with just recognition of the uncertainty of their true etiology. The impossibility of establishing adrenal failure in man by sur-

gical means limited the inclusion of this gland to the rare case of Addison's disease, in which the probable underlying pathology possibly later could be established by necropsy. The very small number of such cases which have been studied prevents that clear-cut definition which the other principal glands possess. The application of the tests to this entire group indicated both the directions and magnitudes of departure from the several base lines, and also established certain norms which were equally significant for the purposes of differential diagnosis.

These standards of performance indicate trends in functional change, the absolute magnitudes being conditioned by the severity of the disease and such intrinsic variables as age, sex, and similar biological factors. The influence of these latter makes it essential, where possible, to express results in relative terms, rather than those of the absolute data from which the relationships derive. For example, basal rates are profoundly influenced by both age and sex, as well as by such other standard measurements (height, area, etc.) as have been selected for correlation purposes. In like manner, the galactose tolerance of the normal female varies throughout the life span, apparently being regulated by the level of sexual activity; the normal male, on the other hand, presents an unvarying level from birth to death. With standards which are themselves variable through biological change, relative values are necessary for any basis of comparison.

In the collation of data certain other factors must receive due and constant consideration. For purposes of clarity, certain terms must be defined in order that in later use they may possess a constant meaning.

The term "hypofunction" is applied to that condition in which all of the clinical and laboratory findings indicate a lowered functional level—the extreme picture of which is produced by complete ablation of the gland—in other words, a state of demonstrable diminution or lack of internal secretory activity.

"Hyperfunction" is used to indicate a condition in which all measurable function levels are of opposite sign to those produced by ablation.

"Dysfunctional" states are those in which evidences of hyper- and hypo-activity are simultaneously observed. Such conditions arise, for example, when endocrine organs initially hyper-

active are undergoing a functional involution to an ultimate hypoactive state. Years ago Cushing (3) called attention to such involutions in acromegaly, and the writer and his associates have frequently observed analogous conditions in thyroid disease. When such involutions occur, all the functions influenced by the gland at fault are not affected at the same rate of speed, and a variety of intermediate pictures is seen, depending upon the degree of the involution at the time of observation.

A second factor in the production of dysfunction lies in the plurality of certain of the endocrine structures. The adrenal, the adult ovary, and the pituitary, all embody certainly two functionally independent tissues, and with the last named yet other possibilities exist. Further, the single gland may produce more than one active principle as the result of its endocrine activities. These several variables naturally can produce a number of intermediate dysfunctional states. With the two extreme functional pictures properly defined, however, these intermediate conditions may be capable of at least a partial analysis.

The third and last phase of the investigation has been the study of the level of function of the individual case. After the careful elimination of all non-endocrine disease conditions which might produce the observed deviations from the norm, the data have been interpreted to define a tentative endocrine diagnosis. Finally, the indicated corrective measures have been applied, under careful clinical control and with repeated laboratory tests, to that gland which has been shown probably to be at fault.

Certain points in the foregoing require brief exposition for the sake of emphasis.

First, no single test can be regarded as significant unless it be checked and controlled by a number of other independent observations. For example, the diagnosis of thyroid disease on the basis of the basal metabolic rate alone is wholly unwarranted. Such a practice could lead to the performance of a thyroidectomy in a case of leukaemia, and certainly has caused the administration of vast quantities of thyroid preparations to individuals with normal thyroid glands.

Second, no single finding suggestive of an endocrine disease should be adduced to support such a diagnosis until all possible non-endocrine causes of the phenomenon have been ruled out by

observation and test. For example, a slight eosinophilia is found in pituitary disease, but should be regarded as signifying such a condition only after the elimination of acute infections, protein sensitivity, skin eruptions, and intestinal parasites—to name but a few among the many. Over-enthusiasm in the interpretation of tests to support an endocrine diagnosis may well lead to the failure to recognize the true underlying cause of the patient's disability.

Third, in the study of each case, careful clinical observation is as important as are laboratory tests. The latter furnish a basis of tested fact for the interpretation of the subjective evidences of the former. But equally, medical history and physical examination offer data which may definitely establish the diagnosis, the laboratory findings serving chiefly as confirmatory supporting evidence. Both are essential, the one complementing and supplementing the other, with the diagnosis resulting from a judicious combination of the factors of each.

One other matter may be briefly considered. In the following pages results will be given from cases exhibiting disease of the pituitary, the thyroids, the gonads, and the adrenals. The pancreas has been omitted since the determination of diabetes—and the writer is in accord with Allen (4) in the limitation of this term to the syndrome caused by failure of the islands of Langerhans—does not usually require so elaborate a procedure as that to be described. The parathyroids have also been omitted because but little is known concerning the disease picture produced by disturbance of their function. On the one hand, several different causes may produce a low blood calcium, and on the other, the correlation of certain disease states with parathyroid inadequacy rests solely on unchecked speculation. In a recent treatise on these glands, Vines (5) reviews a series of conditions said by some to be benefited by parathyroid therapy that would place this product in successful competition with any of the six best sellers of proprietary origin.

A few glandular structures, such as the pineal, thymus, and spleen, are to be regarded as on the borderline, their place in the endocrine family by no means firmly established. Yet other tissues seemingly enjoy their endocrine status through the brevet conferred upon them by the manufacturers of pharmaceutical preparations.

The pluriglandular group, discussed in the later pages, is made up almost without exception of cases in which surgical intervention in one endocrine gland is superimposed upon functional aberration in another. In a series of nearly 3,000 cases the writer has seen but two or three in which there has been apparently a coexistent primary disturbance in more than one endocrine gland. With this truly insignificant proportion, common sense would ascribe the failure to define a single primary focus rather to the lack of knowledge of the observer than to the existence of the conventional pluriglandular syndrome. This statement is not intended to deny the possible existence of a true pluriglandular state, but only to emphasize the essential rarity of such a condition. True, the endocrine glands are among the powerful regulators of the general body metabolism, and failure of any one of them engenders functional derangement in other endocrine and non-endocrine tissues alike. This relationship is one of sequence and does not determine a pluriglandular syndrome in the conventional sense. Further, treatment solely of the primary focus—and if the secondary changes be in a reversible phase—if successful, corrects these latter as a result of normalizing the gland initially at fault. A pertinent illustration is the amenorrhoea of pituitary or thyroid origin.

In the latter discussion, the pituitary and thyroid cases are classified as "hyper-", "hypo-", and "dys-functional," in accordance with the definitions discussed above. The gonad cases are all classed as "hypo-functional," and to this exception may be taken. The writer has never seen a case of hyper-gonadism, *i. e.*, one presenting a picture the opposite of that produced by castration. The diagnosis of hypergonadism in cases referred for study is usually found to be based upon a record of a libido in excess of the observer's concept of the normal. Failing one terminal phase, an intermediate dysfunctional state is hard to define. For this reason, the writer has adopted the simplified classification, recognizing the limitation of its use. For similar reasons, the adrenal cases are also grouped in the single category. There is perhaps even less warrant for this, but if it errs, it is on the side of conservatism.

As the work was first outlined and undertaken, the subjects were admitted to the hospital for a period of seven days, and were thus under control for the duration of the study. The re-

sults of certain tests presuppose an adequate nutritional level, and consequently a diet was outlined to meet this requirement.

As these investigations were not intended to be exact metabolism studies in the sense, for example, of a nitrogen balance measurement, every effort was made to render the diet as varied and palatable as possible. As no exact analysis of the food intake was required, values as computed from Locke's compilation (6) were sufficiently accurate for the purpose. As the writer has elsewhere emphasized (7), such elastic regulation of the diet is of importance in experiments of any duration. The average individual, indifferent alike to the urge of pure science and the enthusiasm of the dietary propagandist, is influenced unfavorably, both directly and indirectly, by the continuance of an unvaried and potentially unpalatable diet. Diets were designed to give at least 6 grams of carbohydrate, 1.5 grams of protein, and a gross energy content of 45 calories per kilogram of body weight. Patients have been permitted to exercise a large degree of freedom in relation to their diet, and in the later studies it has been found necessary only to insure a protein intake above a maintenance level and a carbohydrate allowance sufficient to prevent depletion of the glycogen reserve. In general, the ordinary hospital fare, as outlined by a competent dietician, has been found entirely satisfactory. In isolated cases patients are under special dietary regimen at the time of reference, and this is continued during the hospital stay. For those preferring it, lunch is served at noon and the heavy meal at night. Regulation is secured in the amounts served, not in limitation of the variety.

In connection with the liberal dietary provision, every effort has been made to have the patient's hospital stay depart as little as possible from a normal regimen. Schedules, to be discussed later, are drawn to allow for free hours, and patients are encouraged to go out, see friends, and indulge in reasonable recreation, including theater attendance and other evening diversions. This serves the purpose of minimizing the irksomeness of an enforced hospital stay and, most importantly, produces a state of mind which makes for a maximum of co-operation. In the writer's opinion, this provision should be stressed, as certain of the tests are undoubtedly influenced by the patient's mental state. The more nearly the patients' lives in the hospital compare with

their daily habit, so more nearly are the conditions reproduced under which they have experienced their individual symptoms.

As was intimated above, to conserve the patients' time and yet to permit thorough study, a definite schedule has been drawn up which outlines the sequence of certain basic routine procedures and allows opportunity for the inclusion of a wide variety of special examinations. These latter are selected on the basis of the suggestions developed in the routine examination. Patients are received only on Saturday afternoons, and under ordinary circumstances are discharged one week later. Where certain procedures are found to be necessary which are time consuming and do not permit the simultaneous performance of the routine tests [gastro-intestinal x-ray series, Graham test, duodenal function (McClure), and similar observations], the patient is held over for such additional days as are required. Routine tests are performed in duplicate or even repeatedly, if first results are uncertain. The general form is shown in Table I. It is understood that selections are made from the special examination group to conform with the needs of the individual patient.

TABLE I

GENERAL SCHEDULE ("Long Form")

ROUTINE PROGRAM		SPECIAL EXAMINATIONS
First Day (Sunday)	A. M.	
7:00	Start collection Urine I.	
7:30	Blood I. Complete Morphology.	
7:35	Breakfast. Diet begins (1).	
9:30	Physical Examination.	
	P.M.	
	History.	
Second Day	A. M.	
7:00	Complete Urine I.	Sputum Collection.
10:00	Phenol Sulphone Phtha-	Special Liver Function.
12:00	lein.	Electrocardiogram.
		Endermal Tests.
	P. M.	
12:30	Lunch. Salol I.	Psychometric Examin't'ns
2:30	Adrenalin Mydriasis.	Psychiatric "
4:00	Alveolar CO_2 I. Blood Pressure.	Neurological "
		X-Ray (general).

Third Day A. M.

7:00 Start collection Urine II.
8:00 Basal Metabolism.
Vital Capacity.
Alveolar CO_2 II.
9:30 Breakfast.

P. M.

Respiratory Quotient.
Faeces Collection (2).
Physical Measurements.
Surgical Examinations.
Pelvic "
Otological "

Neuro-Otological Exams.
Ophthalmological "
Audiogram.
Photographs.
X-Ray (general).

Fourth Day A. M.

7:00 Complete Urine II.
8:00 Basal Metabolism.
Spirometer Measurements.
9:30 Breakfast.
10:00 Phenol Sulphone Phtha-
12:00 lein.

P. M.

Repeat second day.

Gastric Function.
Pneumograph Records.
Electrocardiogram.
Polygraph Record.
Cystoscopic Examinations.
Cardiac "
Chest "
X-Ray Pyelograms.

Fifth Day A. M.

5:00 Start Collection Urine G-1.
6:45 Blood II (3).
7:00 Complete Urine G-1, Start G-2.
Test Meal of Galactose I (20 grams).
(+15 gms. Urea in 200 cc. H_2O) (4).
9:00 (5) Complete Urine G-2. Start G-3.
11:00 (5) Complete Urine G-3. Start G-4 (4).
Breakfast.

P. M.

1:00 (Complete Urine G-4)

Neurological (Electrical) Examination.
Audiogram.

Dental Examinations.
Laryngological "
Ophthalmological "
Certain special Examinations of morning of 4th day.
6:45 Blood III for Blood Sugar
9:00 Curve.
(Stool) (2).

Lumbar Puncture.
Special Examinations.
(Phychological.)
(Psychiatric.)

Sixth Day A. M.

5:00 Start Collection Urine G-1a.
7:00 Complete Urine G-1a. Start G-2a.
Test Meal of 5th day (7) ± 10 or 20 gms.
Galactose (10-20% solution).
9:00 (5) Complete Urine G-2a. Start G-3a.
11:00 (5) Complete Urine G-3a.
Breakfast.

6:45 Blood Chemistry II.
Urea Index (R. W.).
Stool (2).
Chest Examination.

P. M.

Lumbar Puncture.
Special Renal Tests.

Seventh Day A. M.

Repeat 6th Day Schedule, changing Galactose Test Meal of 6th day (7) ±5 to 20 gms. Collecting Urines G-1b, 2b, 3b.
11:00 Test ends
or

Omit 3rd Galactose Test and start Gastro-duodenal Function Test (McClure).
Or, Gastro-Intestinal X-Ray Series (6).
Or Graham Test (6).
Or Start Mosenthal Diet for Kidney Function.

P. M.

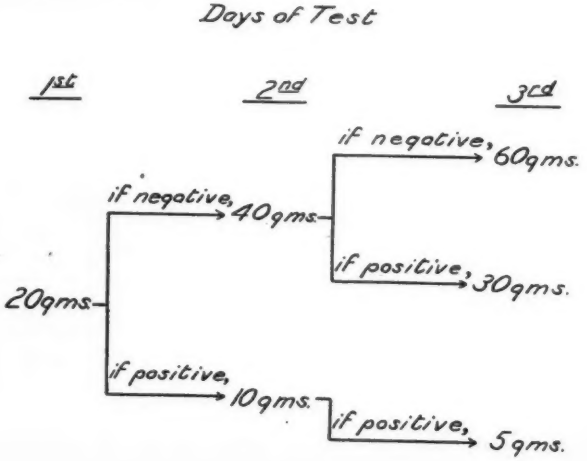
Repeat Phenol, Sulphone, Phthalein.

Eighth Day A. M.

Complete Galactose III or Gastro-Intestinal X-Ray Series (6), or Graham Test (6), or perform Mosenthal Test.

(1) Unless otherwise noted, meals are served at 7:30 a. m. and 12:30 and 5:30 p. m., respectively.
(2) If for blood examination, postponed and diet suitably modified before collection.
(3) Diet of preceding day is creatinin free.
(4) Included only when kidney function is desired.
(5) Patient remains in bed until 9:00 or better 11:00 a. m.
(6) If both Graham and G. I. Series desired, the former is done first and patient remains in hospital until completion of second.

(7) Galactose Chart, q. v.



The scope of certain of the examinations listed above is given in the next table.

TABLE I-a

Urine—I and II	G-1, 2, 3, 4; G-1a, 1b, 1c; 2a, 2b, 2c	
Complete Routine	Sugar	Sugar
Nitrogen Partition	Urea	
Microscopy of Sediment		
"Urobilinogen"		
Special test as indicated		
Blood—I	II	III
Morphology	Morphology	Sugar
	Serology	Urea
	Chemistry	
	N. P. N.	
	Urea	
	Uric Acid	
	Creatinin	
	Sugar	
	Special tests as indicated	

While the method of study outlined above gives a large amount of correlated information, it is time consuming, and moreover, the enforced hospital stay is a definitely limiting condition. Further, the underlying etiology in a number of cases can be determined with a much less elaborate and detailed examination. To meet this need, an abridged schedule has been outlined, embodying certain essential features of the longer study, and this "short form" has proven most helpful in the resolution of diagnoses. The essential features are given in the next table.

TABLE II

Abridged Schedule ("Short Form")

The patient reports at the hospital at 8 a. m. (or somewhat earlier) in a fasting state, and bringing the full 24-hour collection of the urine completed on that morning. After a suitable period of rest, the following schedule is carried out:

8:00 A. M. Basal Metabolism (first measurement at 8:30 or later).
Vital Capacity Measurements.
Alveolar Carbon Dioxide.

9:00 A. M. Injection of Phenolsulphonephthalein.
Physical Examination.
Medical History.

10:00 A. M. First P-S-P Collection.
Blood taken for
(a) Morphology
(b) Chemistry
(c) Serology.

11:00 A. M. Second P-S-P Collection
Special Examinations and Consultations.

1:00 p. m. Patient discharged.

A light breakfast may be served after the blood specimens have been taken. By systematic arrangement several special observations and consultations, as suggested by the history and physical examination, can be performed on the morning of the test. If many observations are required, or if lengthy operations such as x-ray studies of the gastrointestinal tract or the duodenal function are required, return on a later day may be necessary. The sugar test can be carried out at home, each set of samples being sent at once to the hospital for analysis and the next dose of sugar, as indicated by the latter, sent back to the patient.

The degree of definition obtainable by the two procedures is interesting. Under present conditions, less than 3 per cent of the patients undergoing the week's study ("Long Form") are discharged as unclassified, and many of these are partly resolved. For example, five patients in this group giving data indicative of either pituitary disease or of neuro-syphilis refused the lumbar puncture, which would probably have resolved the question. Similar conditions would account for several of the remainder.

On the other hand, in a recent series of 500 patients receiving the morning study, 153 were reported at first as unclassified, and certain additional tests were requested. In 91 of these cases further study established the diagnosis. The greater part of the remaining 62 would undoubtedly have been resolved had the requested supplementary information been forthcoming.

In considering the results obtained in this series of 1,000 cases, certain facts must be borne in mind. With the large number of data involved in the evaluation of each case, a statistical

method of presentation is imperative. As, however, each diagnosis rests upon the interrelationship of the many individual facts recorded, such a general compilation in some measure defeats its own end and tends to obscure the real findings. To illustrate: A nephritis coexisting with an ovarian failure may cause a rise in blood uric acid not characteristic of the latter condition and suggesting pituitary disease, in which such an increase is really significant. In certain dysfunctional conditions the blood may be strikingly lymphoid or leucoid, depending on the type and phase of the dysfunction. In any summary these opposing conditions tend to compensate each other and mask the really significant divergences. By judicious selection, a group of extreme hypo- and hyper-functional thyroid cases could be assembled in which the algebraic sum of the basal rate deviations could be ± 0. On the other hand, due allowance for all the factors operating entails so great a complexity in presentation as to produce an equal obscurity.

Another unavoidable and hampering condition lies in the fact that in a given group departures from the normal reflect in large degree the severity of the condition. The inclusion of a number of incipient and mild cases tends to minimize the positive definition of a trend which will be strikingly shown by the individual advanced case. In the subsequent papers in which individual glands only will be discussed, these objections are partly met by greater detail in presentation; even so, they cannot be eliminated, and in the present paper they operate in full force.

With due recognition of the unavoidable limitations of the method of presentation, the data may be discussed in detail.

As was stated earlier, the present paper aims only to present the general method with such supporting data as may be recorded in significant form. Many informative details must be reserved for the subsequent papers.

HISTORY

Under this caption will be considered only those points which may assume significance for the diagnosis of endocrine disease. At the risk of redundancy, the writer wishes to reiterate that there is no one of these points that may not equally be the result of some non-endocrine disease. Their incidence, however, is of

sufficient frequency to suggest possible endocrine disorder. That all episodes should be dated to establish chronological sequence, should not require comment.

(a) A family history of established endocrine disease is of interest. There seems to be what may best be described as a "constitutional tendency" for the recurrence of endocrinopathies in a given familial line. Many such are recorded in the literature, and there are several striking examples in the writer's own experience. (See Family "C," in the later Thyroid paper.)*

(b) The patient's own past history is most significant. Many endocrine conditions seem to date from severe infections. At the present time the number of individuals who seemingly exhibit sequelae of the severe influenza of 1918 and 1919 is striking. Earlier history of jaundice may help to clarify an anomalous sugar tolerance in thyroid failure. Trauma is always suggestive if involving an area associated with an endocrine gland. Rapid changes in weight, periods of over- or undergrowth, modification in facial contour or increase in size of hands or feet, loss or overgrowth of facial and body hair, are all possibly significant. The foregoing serve merely as illustrations. Many other suggestive evidences will be found in a well compiled history, and the reader can supplement any list as his own experience warrants.

(c) Headache is a frequent finding in this group of disorders, and seemingly confined to no one of them.

(d) Progressive deafness, without demonstrable anatomical change, has been shown by Drury (8) to be associated with endocrine disease in some two-thirds of the cases studied.

(e) A fatigability wholly disproportionate to recorded mental or physical exertion seems to be a cardinal point in the endocrine picture. One hesitates to crystallize this into a formula, but in the main there is a low level of vigor on arising, an improvement to some apex as the day progresses, and then a rapid decline to a level equal to or even below that of starting. Adrenal deficiency is an exception in that rest determines the high levels and exercise their rapid subsidence.

* Recognition of this tendency does not imply subscription to the genial views of those writers who resolve all ethnic traits into manifestations of individual endocrine dominance. While such speculations are diverting, the exclusion of demonstrably powerful biologic forces, the complete absence of any objective supporting evidence, and the resolute elimination of all contradictory evidence, render them unconvincing.

(f) Gastrointestinal disturbances are frequently encountered. Ptosis, poor appetite, and constipation characterize the hypofunctional states, while the converse may obtain with hyperfunction of the pituitary, and especially the thyroid. Polydipsia and polyphagia are conventionally referred to pituitary disorders, but they may be found in both thyroid and, less frequently, ovarian cases.

(g) Unexplained pain in the lumbar region is frequently found in hypothyroid cases.

(h) The menstrual function is peculiarly susceptible to endocrine influences. Late onset of the catamenia, irregularity, scanty or profuse flow, and amenorrhoea and early menopause, are all features of endocrine disturbance. In pituitary and ovarian disease, the tendency is seemingly toward increase in the interspace with scanty flow; with the thyroid, the latter may be profuse and the rhythm increased or diminished.

(i) Sterility. For some time past the author and his associates have been carrying out elaborate studies on the numerous factors concerned in failure of reproduction. Among these, endocrine disorders take an important place, both by the determination of anatomic impedences as the result of abberrant growth, and also through functional disturbances which influence the viability of the sex cells. In this later series, the pituitary, thyroid, and gonad are apparently operative in the order named. A history of miscarriages, with chronological detail, is of primary importance.

(j) Nervous instability and irritability are again among the most common findings. Without seeking a definition which is phantastic, it may be said that the victims of ovarian failure frequently present an active, insistent egocentricity, testicular loss or failure leads to profound mental depression, and the intense nervousness of the hyperthyroid may also be found in the hypofunctional case or merge to a less aggressive selfishness that expresses itself in a sullen truculence. The pituitary patients seemingly more nearly approach the normal level of nervous balance.

(k) Speculation as to the etiology of psycho-neuroses and psychoses, in recent years, has been dominated by two schools of thought, one of which concedes only an endocrine cause, while the other with equal vigor abjures all but psychogenic back-

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grounds. Both theories are probably right in some measure. Certainly the writer has studied a few cases in which a frank psychosis co-existed with an equally demonstrable endocrine malfunction; in some of these both disorders were seemingly corrected by the indicated glandular treatment. Equally, other mental cases have shown a physical normality that eliminates any endocrine disease. It is as unwarranted to express all mental disease in an endocrine formula as to deny the influence of physical conditions on the state of mind. In a subsequent paper the writer will offer one or two striking cases illustrating each contention.

Aberrations of temperature response, such as hypo- and hyperthermia, are frequently found in thyroid disease and not unknown in other endocrine states.

The above constitute some of the suggestive points which may be derived from a well-ordered history. No attempt at completeness is possible within the scope of a journal article.

PHYSICAL EXAMINATION

Of necessity, this section deals chiefly with trophic evidences. A principal value of the physical examination is to indicate the existence of non-endocrine disorders to which the patient's disabilities may be ascribed. Only occasionally will the findings be positively suggestive of endocrine disease.

(a) The general body habitus, and particularly the relation of individual segments to each other or to the whole, are of real significance. Draper (9) has spent years in the study of such correlations and has gathered together a massive array of data which are most suggestive. It is to be regretted that others with the same fine enthusiasm lack the temperate reserve in interpretation that marks his concluding paragraphs (l. c., p. 222). Disproportion engendered by overgrowth before epiphyseal union has taken place or, equally, by premature closure, is highly suggestive in its measureable results.

(b) The localized distribution of obesity—as the girdle type found in pituitary disease, the fat body with thin legs of the patient with ovarian failure, and the generalized distribution in the hypothyroid individuals, really constitute a part of the foregoing. True, they are seldom realized in classic type, but they do define suggestive trends. The degree of obesity may make

them all apparently merge in the thyroid type, as in a case of the writer's, a boy with pituitary failure who was less than five feet tall and weighed 400 pounds. Emaciation also may be suggestive where the loss has been selective.

(c) The amount and distribution of body hair with tendency to inversion in type of this secondary sex characteristic is significant. Each of the glands may produce one or more characteristic pictures.

(d) The spacing, development, and general appearance of the teeth should be carefully recorded. They may suggest disorders of the pituitary or thyroid or call attention to such conditions as rickets and congenital syphilis.

(e) The shape of the nose may be suggestive of an endocrinopathy. The characteristic forms in acromegaly and cretinism are illustrations.

(f) Marked asymmetry of the face and, less frequently, of other portions of the body, may suggest those growth anomalies resulting from metabolic derangement.

(g) The shape, appearance, and consistency of the finger nails undergo modification, particularly in thyroid disease.

(h) The general character of the skin and the presence of skin eruptions should always be noted. With even the meager knowledge of today, it seems possible that endocrine disease may engender certain trophic changes in the skin, possibly by indirect influence on the general metabolic level. Myxedema in thyroid failure is the prototype.

(i) A tendency toward the development of varicosities in the lower limbs has been noted in pituitary disease.

(j) Evidences of thyroid enlargement are as apt to be misleading as they are helpful. The diagnosis of thyroid disease on the unsupported evidence of a goiter has done and is doing grave mischief.

(k) Aberrations of vision can best be considered under a later caption, and this is true also of slow and rapid pulse rate, and changes of body temperature, blood pressure, and certain other physical measurements.

Again, in concluding this section, emphasis is laid on the illustrative character of the items selected, and even more strongly on the fact that they are never more than suggestive. Final diagnoses should not rest on the appearance of the eye-

brow nor on an obesity deriving from what may be designated with courtesy as a good appetite.

Turning next to the laboratory findings and with reminder of the limitations imposed by tabular summation, the relative composition of the series may be considered.

TABLE III

DIAGNOSTIC SUMMARY

Diagnosis	Number of Cases		Per Cent	Group Per Cent
	Series B	Series S		
Not Endocrine	79	211	29.0	29.0
Pituitary, hypo- (−)	28	35	6.3	
dys- (±)	113	103	21.6	28.4
hyper- (+)	5	0	0.5	
Thyroid, hypo (−)	22	50	7.2	
dys- (±)	14	21	3.5	12.4
hyper- (+)	0	17	1.7	
Gonad, hypo- (−)	55	89	14.4	14.4
Adrenal, hypo- (−)	10	3	1.3	1.3
Pluriglandular, hypo- (−)	2	2	0.4	1.8
dys- (±)	6	8	1.4	
Unclassified, endocrine	6	63	6.9	12.7
doubtful	10	48	5.8	
Totals	350	650	100.0	

Too great significance should not be given to the relative magnitude of any group. The cases were all seen in a consulting diagnostic service, and in many instances the patients did not require elaborate studies to determine the underlying etiology; thus certain classes find but scant representation in this series. This is particularly true of the hyperthyroid group in which the presenting clinical picture, with its characteristic features, together with the history, physical examination, basal metabolism, and blood morphology, usually suffice to establish the diagnosis. At the most, the abridged study (Short Form) was adequate.*

The relative infrequency of demonstrable adrenal cases is strikingly shown. These represent the residua of a much larger group submitted in which bronzed diabetes or primary anaemia was found to be the true condition.

* In a very few subsequent cases the longer study has been carried out. In all of these, non-endocrine diagnoses had been established elsewhere, and only complete investigations would permit a certain resolution of the question.

Considering the stress laid upon so-called pluriglandular syndromes, to say nothing of the widespread use of pluriglandular therapy, the figures here presented are worthy of remark. A further analysis of the eighteen cases offers yet more salient facts. These are presented in tabular form.

TABLE IV

ANALYSIS OF PLURIGLANDULAR CASES

Gland Involved	Surgical Cases	Total Cases
Pituitary	0	12
Thyroid	5*	11
Gonads	10*	12
Unknown	0	1†

SUMMARY

Etiology	No.	%
Surgical Cases	13	1.3
Doubtful†	1	0.1
Functional or organic.	4	0.4
Total	18	1.8

* Two patients had both ovaries and part of the thyroid removed.
† Mongolian idiocy.

Summarized, all but five of these cases derive their plural character from the interposition of surgery, and of these one, that of a Mongolian idiot, has only a conventional claim to inclusion; a second is a patient with thyroid failure in middle age who had seemingly an overactive anterior lobe in the prepuberal years. The whole question will be discussed in detail in a subsequent paper.

A few points, only, require comment. The designation of the degrees of activity of the several glands has already been discussed.

It is significant that in a series of 1,000 cases, in the main carefully selected as presenting evidences of probable endocrine disease, nearly one-third demonstrated a definite non-endocrine condition to which the presenting symptoms could be referred.* This fact emphasizes the unwisdom of the establishment of an endocrine diagnosis on purely clinical evidence alone, and, as a corollary, the necessity of eliminating disease condition unassociated with the ductless glands before interpreting data in terms of endocrine disease.

The incidence of pituitary cases seems to exceed either the thyroid or gonad by a ratio of 2 to 1. As has been pointed out,

* In the next 1,000 cases the non-endocrine percentage was 39.6. This was influenced in some measure by the study of certain special disease groups to ascertain if there were an endocrine element in their etiology. Deleting these cases, the remainder constitute about one-third of the whole.

this is not strictly accurate as regards the thyroid, and the gonad figures are possibly influenced by the relative infrequency of male patients. As will be considered elsewhere (this article and a later paper on the gonads), the testicle in adult years, in contradistinction to the ovary, seemingly exercises but a meager influence on the general metabolic level. The individuals here presented were chiefly castrates, who have co-operated in the work, or were patients referred for sterility following a non-venereal disease. Within these limitations the figures as given possess a certain general significance. The predominance of the dysfunctional type of pituitary is interesting.

The larger number of unclassified cases in the "Short Form" group illustrates the value of the additional tests. Had opportunity been given for further study, many of them could have been resolved, as has been pointed out above. More extended experience also tends to make the undetermined group smaller.

The next table presents some of the purely physical measurements and illustrates the wide range of the cases studied. As these are based on absolute values, they emphasize the worst features of collective presentation. All measurements are made on the nude subject and are determined with standard anthropometric equipment. Lung volumes are measured with a calibrated water-sealed spirometer of standard type.

The numerical preponderance of the female in the endocrine group contrasts with the relatively greater equality in the non-endocrine. In the main this agrees with other records, only the pituitary proving an exception. While the tallest case is in the pituitary group, the average corresponds to that of the entire series and is less than that of the non-endocrine section. The relative average age shows that this is not referable to an undue proportion of children. The age averages are in substantial agreement with the observations of others. The slightly greater age of the pluriglandular group reflects probably the time factor in the causation of the surgical element to which they are referable. The sitting height indices show a very definite uniformity. They are influenced by the female preponderance in absolute magnitude, and striking individual departures are lost in the summary. The failure of the gonad (and the pituitary) group to show a low value is due presumably to the fact that cases presenting disease in adult years dominate the series. In the

TABLE V

PHYSICAL MEASUREMENTS

Observation		Unit	Endocrine Group							Not End.
			Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Sex	Male	%	37	22	5	23	0	16	24	42
	Female	%	63	78	95	77	100	84	76	58
Age	High	years	70	74	63	62	63	61	74	78
	Low	years	6	8	13	7	17	7	6	9
	Average	years	33	37	33	35	41	32	33	38
Height	High	cm.	195	184.5	174	177	188	181.5	195	193
	Low	cm.	103	131.5	148	115	146	113	103	139
	Average	cm.	164	162	162	162	166	160	163	165
*Sitting Height	High	cm.	100	96	94	96	95	92.5	100	99
	Low	cm.	56	75	77.5	64	80.5	62	56	72.5
	Average	cm.	87	86	86	85	88	85	86	87
Sitting Height Index			0.530	0.531	0.531	0.524	0.530	0.531	0.530	0.527
Chest	High	cm.	150	107	121	107	110	111.5	150	125
	Low	cm.	54.5	62.5	60	56	63	50	50	59
	Average	cm.	81	80	78	73	83	79	80	80
Weight	High	kgm.	164.1	124.5	124.0	89.0	128.0	113.0	164.1	145.0
	Low	kgm.	15.7	31.3	35.8	22.0	41.2	15.6	15.6	28.1
	Average	kgm.	67.4	61.8	62.0	52.6	70.0	62.9	64.4	61.5
Area	Average	sq. m.	1.73	1.66	1.66	1.55	1.78	1.66	1.69	1.67
†Lung Volume	High	c. c.	6200	4640	4940	4100	3200	4520	6200	5500
	Low	c. c.	600	820	930	1700	1140	800	600	300
	Average	c. c.	2960	2550	2710	2460	2440	2550	2760	3020

*Designated as "Trunk" by Dreyer. †Designated as "Vital Capacity" by Dreyer.

weight averages, the pituitary and pluriglandular groups (in the latter a pituitary influence is dominant) are well above the mean, while the emaciation of the adrenal cases is equally clearly defined. All of the endocrine cases save the pituitary, show values for the lung volume significantly below the non-endocrine group. Absolute values here are influenced by several extraneous factors which do not appear. The seeming diminution is in part apparent rather than real (see adrenal cases in next table), and in the main is probably due to the asthenia which is a character-

TABLE VI
"VITAL CAPACITY" COMPARISONS

Observation	Endocrine							Not End.
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	Total	
Weight—								
High	+247%	+ 82%	+107%	+ 19%	+ 78%	+ 67%	+247%	+ 75%
Low	− 42%	− 29%	− 37%	− 36%	− 14%	− 36%	− 42%	− 35%
% above normal	62	57	55	25	65	55	58	48
Average	+ 29%	+ 23%	+ 24%	+ 16%	+ 24%	+ 26%	+ 26%	+ 17%
% below normal	38	43	45	75	35	45	42	52
Average	− 12%	− 15%	− 11%	− 19%	− 9%	− 13%	− 13%	− 12%
Total average*	+ 13%	+ 8%	+ 9%	− 10%	+ 12%	+ 9%	+ 10%	+ 2%
Chest—								
High	+ 96%	+ 36%	+ 66%	+ 15%	+ 43%	+ 47%	+ 96%	+ 36%
Low	− 24%	− 23%	− 17%	− 17%	− 18%	− 13%	− 24%	− 23%
% above normal	64	53	47	25	75	60	57	58
Average	+ 12%	+ 12%	+ 13%	+ 12%	+ 16%	+ 14%	+ 13%	+ 9%
% below normal	36	47	53	75	25	40	43	42
Average	− 7%	− 7%	− 7%	− 10%	− 10%	− 7%	− 7%	− 7%
Total average*	+ 5%	+ 3%	+ 2%	− 5%	+ 10%	+ 5%	+ 4%	+ 2%
Lung Volume—								
High	+ 18%	+ 12%	+ 23%	± 0%	− 11%	+ 17%	+ 23%	+ 17%
Low	− 62%	− 75%	− 67%	− 29%	− 60%	− 58%	− 75%	− 89%
% above normal	11	9	10	8	0	6	10	17
Average	+ 6%	+ 7%	+ 7%	± 0%	− 0%	+ 12%	+ 7%	+ 5%
% below normal	89	91	90	92	100	94	90	83
Average	− 22%	− 28%	− 22%	− 19%	− 27%	− 24%	− 23%	− 26%
Total average*	− 19%	− 25%	− 20%	− 17%	− 27%	− 22%	− 21%	− 21%

*Weighted for number of cases.

istic of endocrine disease in general. As was stated above, in many cases absolute average values are not greatly informing; relative quantities tend to place greater emphasis on significant differences. In the next table are collated values derived from the Dreyer (10) and West (11) comparisons. With the former, only those correlations based upon sitting height ("trunk") are considered, as the author's formulation presupposes a relatively normal configuration, and in cases of obesity leads to impossible extrapolations. Further, but one occupational standard instead of Dreyer's three has been used, as by so doing disturbing com-

plications are avoided. The whole matter has been discussed by the writer (12) in another place. Experience in this country shows that the "A" male and "B" female standards most nearly conform to average experience. In the West comparisons, for like reasons, only the male and female standards are used. In both series, children (boys and girls) are referred to the female standards, as experience has shown this to be most representative. The values presented in the table for Lung Volume ("vital capacity") are the averages of the Dreyer and West comparisons.

In the table above, "High" and "Low" represent the deviation from prediction in the two extreme cases in the group. The relative number of the group above and below prediction are indicated by percentages and the average deviation of each group is appropriately placed. The total average is the algebraic summation of the two groups suitably weighted for numbers. To illustrate, the heaviest pituitary case was 247 per cent above prediction (+), and the lightest 42 per cent below (—). Sixty-two per cent of the group were overweight, the average being 29 per cent above prediction (+), while the remaining 38 per cent were underweight, their average being 12 per cent below prediction (—). The whole pituitary group showed an average of 13 per cent above (+) prediction.

With the weight comparisons, the dominance of the pituitary and pluriglandular groups in part disappears, but the emaciation of the adrenal cases gains in emphasis. The chest values are indeterminate. The lung volumes in the total endocrine group exactly equal those in the non-endocrine. Of the individual components of the endocrine group, the thyroid and pluriglandular groups are most affected, the pituitary and, surprisingly, the adrenal* the least. The lowered lung capacity in the thyroid cases has already been commented on, and a number of years ago Bryson (13) called attention to the lessened chest expansion in thyroid disease. With the pluriglandular group it is possible that the low values reflect the influence of the twofold endocrine disorder which they present. Too great weight should not be placed upon lung capacity measurements, however, since the degree of co-operation of the subject influences the magnitude unduly. It is safe to say, nevertheless, that thyroid disease

* The small number of cases composing this group makes this observation less significant than in the case of values for the other series.

causes a diminution in this quantity that is of potential diagnostic significance.

The general examination of the urine offers numerous points of interest. Many of them cannot be reduced to presentation in tabular form, but certain significant measurements are grouped in the next table. Of the methods selected, that of Ehrlich (14) for the so-called "urobilinogen," the amylase method (15)* and the standard method for salol may be mentioned. The values for the "phthalein" test were obtained by comparisons with graded standards in a du Bosq colorimeter. The urea curve was determined by four two-hour collections following a test meal of 15 grams of pure urea taken in a fasting state and following a two-hour control collection. Folin's (16) method was used for the analyses.

TABLE VII.

URINE DATA

			Endocrine				Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Uncl.	End.
Volume .....Av.	1230	1110	1130	1140	1440	1220	1260
Specific Gravity.Av.	1.019	1.019	1.019	1.016	1.016	1.019	1.018
Albumin, % positive	22	20	19	69	28	9	17
Casts, % positive	16	16	17	23	11	13	15
Sugar, % positive	24	12	27	23	33	16	10
"Urobilinogen" % positive	36	3	0	0	22	16	2
Amylase Index.Av.	18	16	16	13	18	11	14
Salol (minutes).Av.	74	91	88	96	90	61	79
Urea Curve, Normal	71%	80%	86%	28%	83%	..	80%
Low	29%	20%	14%	72%	17%	..	20%
P-S-P,** 2-hour Total Av.....	50%	55%	54%	50%	53%	53%	53%

Considering first the urine volumes, it is evident that the pituitary does not exhibit any striking augmenting influence. Naturally, in the series a number of patients exhibited polyuria, but a compensating oliguria was shown by others. As the work of Camus and Roussy (17), Houssaye (18) and, most recently, Bourquin (19) has thrown some doubt on the unique influence of the pituitary as the direct causative agent in diabetes insipidus, this is rather to be expected. The lowering influence of

* Later discontinued, as other methods of evaluating kidney function were found to be far more significant.
** Phenolsulphonephthalein.

thyroid and adrenal failure is here shown as a tendency. The low gonad value is in part ascribable to the overwhelming predominance of females coupled undoubtedly with a tendency to lessened elimination. Only the adrenal group shows a marked decrease of dissolved matter ("total solids"), though many individual cases of thyroid failure exhibit the same tendency. The healthy appetite of many of the thyroid subjects tends to mask the lowered metabolic level which undoubtedly exists in failure of this gland. It will be remembered that the hyperthyroid group in this study is too small to influence the summated results. While albuminuria is a frequent observation in the entire series, its dominance—and in less degree the incidence of casts—in the adrenal cases is a marked evidence of the nephritis, which is a usual feature of this condition. In general, however, in the endocrine cases, albumin and casts may be regarded rather as evidences of disturbed kidney metabolism than as indicating the existence of true nephritic states.* A striking observation is the relative frequency of glycosuria in the endocrine group. Overactivity of the posterior lobe of the pituitary (but not underactivity as recorded by several writers), hyper- and dys-functional states of the thyroid, and ovarian failure have frequently been recorded as causal conditions. The lower percentage in the thyroid group rests on the relatively lesser influence of this gland on carbohydrate metabolism. This will be considered later under "Sugar Tolerance." The writer's findings with adrenal failures are not in accord with the frequently expressed opinion that this condition raises sugar tolerance. Reference will be made to this point later, both in this and in a subsequent paper. Another interesting feature is the not infrequent appearance of glycosuria in the non-endocrine group. It is to be remembered that pancreatic cases were excluded from this compilation. The easy assumption, so frequently recorded, that glycosuria indicates an incipient diabetes (that of pregnancy, for example) is but a persistence of the erroneous concept of unitary control of body functions. Lesions of the central nervous system (without other evidence of indirect pituitary involvement), syphilis, liver disease, primary anaemia, leukaemia, and cancer, are all represented in the group

* In the subsequent paper on the thyroid, emphasis will be laid on the "pseudo-nephritis," which we have already recorded in this condition.

here recorded. This question, too, will be discussed in detail in a later paper.

A positive "urobilinogen" test stands out definitely in the pituitary group or in those series such as the pluriglandular and "unclassified" in which this gland is or could be a factor. In the positive thyroid cases there was a concomitant liver dysfunction, while this latter condition and primary anaemia were responsible for its appearance in the few non-endocrine cases. When they can be excluded, the test offers one fact toward a pituitary diagnosis. The non-specificity of the test as an evidence of the presence of urobilinogen has already been touched upon.

The amylase test falls short of any real significance and in the later studies has been discontinued. Salol is a rough measure of gastric motility, if kidney function be demonstrated to be normal. It is included for its possible information in the sugar tolerance test. The lowered kidney permeability of the adrenal cases is also revealed in the urea curve. The observations of this laboratory would indicate that an inadequate level of protein metabolism may be a source of error in the results of this test. Whether through tissue absorption of urea or through some other agency, the fact remains that many patients with a partial protein inanition and demonstrably sound kidney function show a low curve of urea elimination under the stimulus of a provocative urea test meal. Blood urea measurements recorded elsewhere (20) indicate that this is not due to failure or delay of absorption. The observed fact is suggestive. The phenolsulphonephthalein values seem only to illustrate the relatively inconclusive character of this test in all but terminal phases of kidney involvement.

Another observation based upon the determination of urine constituents is found in the so-called "nitrogen partition." While under ordinary conditions urea constitutes the major portion of the protein waste, uric acid, creatinin, and ammonia are constantly present* in appreciable amounts, representing end phases of specialized metabolic processes. In addition, there is the undetermined fraction made up of a large number of both known and unknown nitrogen-containing compounds usually

* Exception is noted of the disappearance of the last named when the combining power of the plasma exceeds 80 volumes per cent. (See Fitz and Van Slyke.) (21).

present in small amounts. It should be repeated that this test as performed in this study does not constitute a part of an elaborate nitrogen balance measurement. The first urine examined gives information both as to the daily dietary of the patient and the relative composition of the protein waste. When a second urine is tested—as in the routine of the Long Form—it gives the added information of the influence of the hospital standard dietary on the quantitative performance of the patient, and serves as a check on the first. In the first instance, the total gives valuable evidence on the accuracy of the patient's statement of dietary habit,* and in the second, as will be shown, the items of the partition may assume a diagnostic significance. Total nitrogen is determined by the standard modified macro-Kjehldahl method (using both copper and potassium sulphates), urea, uric acid, creatinin, and ammonia by the several procedures devised by Folin (22). The data are collected in the next table.

TABLE VIII

NITROGEN PARTITION

			Endocrine					Not
Observation	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	Tot.	End.
Tot. Nitrogen. (gms.)	9.57	8.34	8.94	7.46	8.97	9.32	..	9.26
Urea " (%)	80.6	79.0	80.9	79.8	80.0	80.7	80.3	81.1
Uric Acid " (%)	2.0	2.2	2.0	2.2	2.1	2.0	2.1	2.3
Ammonia " (%)	3.9	4.2	3.9	4.7	4.9	3.6	4.0	3.8
Creatinin " (%)	4.4	4.2	4.5	4.0	4.8	4.2	4.3	4.5
Residual " (%)	9.1	10.4	8.7	9.3	8.2	9.5	9.3	8.3
Residual, total % of cases equal or over 9%	45	56	45	54	44	61	49	38

In the table given above, the first line records the average nitrogen elimination of the individuals composing each group, while the next five indicate the percentage distribution among the five components. The last line records that part of the group exhibiting a "residual" or "undetermined" fraction in excess of the conventional normal of 9 per cent. For example, 56 per cent of the thyroid cases showed residual fractions above the normal.

All of the total nitrogen values here presented are above

* This ranges in experience from the obese lady who confesses to one egg and a biscuit or two a day, with 20 grams of nitrogen in the urine, to the equally subjective individual who claims a liberal dietary habit—and shows 3 grams. Body weight is not a safe criterion for estimating protein levels, and a partial inanition of this essential constituent influences significantly the basal rate, the blood chemistry, and other important magnitudes.

the maintenance level and all of them are likewise below that which would correspond to the hospital allowance of protein. (Based on the protein allowance in terms of body weight, this would range approximately from 11 grams in the adrenal cases to 15 grams in the pluriglandular). The discrepancy becomes less when it is remembered that two-thirds of the patients collected their urines at home and that the first urine of the remainder was collected in such manner as to show the home nutritional level. A lowered level of protein metabolism in thyroid and pituitary failure has often been recorded, while the increase in hyperthyroidism is regarded as pathognomonic. The thyroid hypofunction effect is shown here, but an adrenal influence appears even more strikingly. Lowered kidney permeability and the several influences due to asthenia undoubtedly operate here. The pituitary shows the highest level of the several groups, bulimia being one probable factor, but the existence of a generally normal level of many functions in this particular condition being certainly another. In passing, it may be said that while the several types of pituitary disease cause certain strikingly significant departures from the normal, in a number of respects they conform straitly to conventional standards. The differential significance of this will be stressed later.

Turning to the several partition formulas, the only striking irregularity is found in the residual or undetermined moiety. Passing comment may be made on the constancy of the uric acid fraction, a constitutent which Falta (23) found to be increased in the pituitary cases, but which is not demonstrably influenced in this series.

The average value for the residual fraction in normal adults drawn from nearly 400 cases [Folin (24), Mathews (25), Long and Gephart (26), Rowe and Proctor (27)] is just under 6 per cent, with 10.9 grams as the average for the total nitrogen. Folin's original study demonstrated an increase in the relative amount of the residual nitrogen with lowered nitrogen elimination, but the percentage remains less than eight when the nitrogen elimination exceeds five grams. It is true that the residual fraction is determined by difference and so absorbs all of the errors incident to the other measurements, but these would operate equally in all groups large enough to nullify individual differences. Hence such variations as are actually observed must

be significant even though the absolute magnitude may not be rigorously accurate. Further, the use of the best available methods by a group of technically skillful workers offers additional safeguard against gross error. The experience of the writer with several thousand such analyses has led to the adoption of the conventional value of 9 per cent as the upper normal level. Conceivably, this is slightly high, but the adoption of a somewhat lower criterion would serve only to emphasize the endocrine influence. As it is, the endocrine series shows an upward tendency most marked in the thyroid group, which also exhibits the largest percentage of individual cases exceeding the conventional normal limit.* The adrenal comes next and only the pluriglandular group shows an average less than the non-endocrine. Even here the percentage of individual cases showing high values is greater in the endocrine group. Further, the endocrine average is above, that of the non-endocrine group below, the conventional boundary. As the percentage of non-endocrine cases showing high residuals is not strikingly inferior to that of the endocrine group, however, a further analysis of the former is interesting.

Cases of leukaemia, malignant neoplasm, tuberculosis, and epilepsy show very high incidence and very high absolute values. Lower, but still significant, are primary focal infections, such as those of teeth and of tonsils, various lesions of the central nervous system, and primary anaemias.

The underlying mechanisms of this increase are still obscure. A study already reported in brief [Rowe and Proctor (27)], and shortly to appear in detail, demonstrates that while the amino-acid, hippuric acid and creatin fractions all show increase—the first, only, in significant absolute amount—there still remains an undetermined quantity which in the control (normal) group is 3 per cent, in the non-endocrine group about 5 per cent, and in the endocrine group exceeds 7 per cent of the total nitrogen elimination. Further, a determination of the neutral sulphur fraction (as possibly associated with nitrogen-containing molecules) shows no change of significant proportions. In other words, while known constituents of the urine, usually present in small amount, are found to be definitely increased, there remains

* The unclassified cases are, for obvious reasons, omitted from this discussion.

a fraction of unknown composition still to be accounted for. This problem is now under investigation.

As the urine constituents are derived from those of the blood stream, the chemical composition of the latter may next be considered. The routine examination calls for the determination of four nitrogenous constituents and of sugar. Individual cases call for additional observations, but in no series has any other single constituent been measured with sufficient frequency to warrant inclusion.

In the main, the methods outlined in the well-known Folin-Wu (28) procedure have been followed. Urea has been aerated rather than distilled, though both methods are used to control each other. The uric acid method has been varied in accordance with the suggestions later reported (29).

Neither the uric acid nor creatinin procedures are specific for the substances named, and this criticism is equally applicable to the sugar determinations. They all, however, give dependable and reproducible results, seemingly are not grossly in error, and the relative values thus obtained are to be regarded as significant. The collected data are given in Table IX.

TABLE IX

BLOOD CHEMISTRY (and Serology)

		Endocrine					Not
Observation	Pit.	Thy.	Gon.	Adr.	P. G.	Uncl.	End.
Non-Protein Nitrogen..mgm.	33	32	31	38	31	32	34
% over 35 mgm.....	29	26	20	58	25	24	26
Urea Nitrogen.....mgm.	16	15	14	14	16	14	16
% over 17 mgm.....	17	20	19	18	19	10	24
Uric Acid.....mgm.	3.8	3.5	3.3	3.8	3.6	3.4	3.5
% = or over 4.0 mgm. (net)*	34	18	12	22	20	25	11
Creatinin .....mgm.	1.5	1.5	1.5	1.5	1.5	1.6	1.5
Residual Nitrogen.....mgm.	15.1	15.2	15.3	22.1	13.2	16.2	16.2
Sugar .....mgm.	94	98	97	84	96	95	97
% over 120 mgm.....	1	4	4	0	6	2	2
% under 80 mgm.....	5	5	8	50	12	8	5
+ Wassermann .....(cases)	0	1	0	0	1	0	10
+ Schwartz-McNeil .(cases)	1	0	0	0	0	0	0
+ Spinal Fluid.....(cases)	1	0	0	0	0	0	2

*All demonstrated cases of nephritis deducted.

In largest measure the blood picture confirms the observations already made on the urine. Significant variation is shown by the high uric acid in pituitary disease. This is duplicated only in the adrenal group, and here are found other evidences

of kidney disease which are lacking in the pituitary picture. The high residual fraction in the adrenal group is a striking observation possibly connected with the urine findings in these cases. No explanation for the low value in the pluriglandular group is at present known. The relatively greater frequency of high blood uric acid without demonstrable kidney disease lends to the datum a certain diagnostic significance. Hammett and his co-workers (30) observed this phenomenon in a small group of experiments with pituitary feeding. Whether it is due to an increase in uric acid or of some other substance giving the same reaction, remains to be ascertained.*

The hypoglycaemia of adrenal failure, frequently reported, is definitely confirmed in this series. That blood sugars are relatively normal in all of the other endocrine conditions renders this a point of significance for differential diagnosis.

The results of the serological examinations, included in this table for convenience, show nothing striking. The inclusion of the three positive cases in the endocrine group is reasonable, as the pituitary case with positive spinal fluid gave only a doubtful test, while the positive Wassermanns in the single thyroid and pluriglandular cases showed a possible lues superimposed upon unmistakable endocrine disease.

Relatively few reports of blood chemistry in endocrine disease are found in the literature, but the older art and science of blood counting has developed certain conventional formulas for the blood morphology. The lymphocytosis in thyroid, pituitary, and adrenal malfunctions, the eosinophile increase in the two latter, and the increase in large mononuclear cells in thyroid disease have been frequently recorded. Less certainly established are lowered haemoglobin in thyroid and pituitary failure, lowered red count in these and adrenal failure, and leucopenia in the first two. A prevailing high red count has been remarked in acromegaly. The results in this study are grouped in Table X.

No striking deviation in the haemoglobin content is exhibited by any of the groups. The primary anaemia cases were too few to influence the average in the non-endocrine group. The red count shows a surprising uniformity. Naturally, individual cases with well-marked secondary anaemia are absorbed in the

* In a few observations by the modified Folin method (31), the uric acid amounts continued relatively high.

TABLE X

BLOOD MORPHOLOGY

Observation	Endocrine						Not
	Pit.	Thy.	Gon.	Adr.	Pl.Gl.	Uncl.	End.
Haemoglobin, %.....	89	87	90	87	91	90	88
Erythrocytes (1,000,000)...	5.11	4.92	4.98	4.79	5.09	4.95	4.93
Leucocytes (1,000).....	7.7	7.7	7.7	7.0	7.7	7.2	8.0
DIFFERENTIAL COUNT							
Polymorph. Neutrophiles, %	57	56	57	51	59	57	62
% = or over 75 %.....	5	3	6	8	6	3	7
Lymphocytes	35	37	35	40	35	35	30
% = or over 33 %.....	58	61	54	62	65	59	38
Eosinophiles	3	2	2	2	1	2	2
% = or over 3% (net)*.	30	25	21	39	6	17	14
Endothelial Leucocytes....	5	5	6	7	5	5	6
Abnormal Erythrocytes...	0.5%	2%	0	0	0	0	2%

average, but with so large a number the tendency toward relative normality would seem to be established. The leucocyte counts are a low normal, in every case somewhat below the non-endocrine group, and reaching possibly significant proportions only in the adrenal cases. The cases of leukaemia were omitted from consideration in deriving the leucocyte formula. An upward trend of the lymphocytes is unmistakable throughout the entire endocrine group, and is most marked in the pluriglandular fraction. Slightly over one-third of the non-endocrine cases show a lymphocytosis as against about 60% for the endocrine group. Pituitary disease seemingly tends to produce a mild eosinophilia, while two-fifths of the adrenal cases exhibit it. A like influence is somewhat less strongly shown in the thyroid section. Broadly speaking, the chief departures from the normal are a general trend toward lymphoid bloods and a slight eosinophilia more marked in pituitary and adrenal cases. As a matter of fact, the eosinophilia in pituitary disease is in our experience somewhat more striking than the tabulation would indicate. It suggests a tendency, however, rather than an established condition. The increase in lymphocytes in the non-endocrine cases shows certain well-marked etiological relations. Malignant neoplasms, tuberculosis, focal infections, syphilis, and the blood diseases, exhibit the condition in a significant percentage of the cases observed. As will be remembered, these are substantially the same condi-

* All cases showing acute inflammatory process, skin eruptions, protein sensitivity, and intestinal parasites, were omitted.

tions in which the interesting but non-specific high residual nitrogen fraction was manifested. In the endocrine group over 50 percent of the cases exhibit one or both of these anomalies, while nearly 40 percent of the non-endocrine fraction show the same deviation. The correlation of the incidence of these two abnormalities is interesting.

TABLE XI

CORRELATION OF HIGH RESIDUAL NITROGEN AND LYMPHOCYTES

DIAGNOSTIC GROUP	Residual Nitrogen Lymphocytes	Above Normal Normal	Normal Above Normal	Above Normal Above Normal
Endocrine				
Pituitary	(%)	17	30	28
Thyroid	(%)	21	26	36
Gonads	(%)	20	27	26
Adrenals	(%)	23	31	31
Pluriglandular	(%)	12	35	29
Total Endocrine*	(%)	19	30	30
Not Endocrine	(%)	25	25	13

Inspection of the table shows that in the endocrine group there is a relatively low incidence of high residual nitrogen alone. Patients showing lymphocytosis, and those in whom both appear are practically 50 percent more frequent in occurrence. The non-endocrine group exhibits an opposite relation as the coincidence of the two abnormal findings is but half of the incidence of each alone. We make no attempt at this time to explain the significance of this observation. The facts are reported as they occur. It may be permitted to comment, however, that on the basis of probability, cases showing both are about 2.5 times as likely to demonstrate an endocrine etiology.''

During recent years the respiratory metabolism has played a most important part in the evaluation of endocrine conditions. The establishment of normal levels begun by Atwater and Benedict (32) and continued by the latter and his later associates, in a long series of fundamental contributions, has made possible the determination of the significant variations produced by disease. Studies of the influence of disease on oxygen consumption,

* Unweighted averages. Weighting gives the practically identical values of 19-28-30.

** The unclassified cases, the great majority of which were probably endocrine, show the values 18-21-34. The endocrine element is here manifested as a tendency.

practically initiated by Magnus Levy (33), but developed principally by Du Bois and his associates (34), have shown that deviations of the so-called basal metabolism may assume a most important diagnostic significance. The profound influence exercised by the various types of thyroid disease has somewhat overshadowed, in the minds of many, the definite influence exercised by other members of the endocrine group as well as by a variety of disease states unassociated with the ductless glands.

Two clinical methods are available for this measurement, both depending on the measurement of the gas exchange. In the open circuit procedure the expired gases are analyzed both for carbon dioxide and for oxygen and the energy exchange calculated from the oxygen consumption, with due allowance for the ratio of the two. In the closed circuit method, oxygen is rebreathed after removal of the expired carbon dioxide and the energy exchange calculated from the oxygen as measured, with the assumption of a constant (0.82) respiratory quotient.* Both methods number staunch supporters among the productive workers of this country and much polemical literature exists in which the relative merits of each are vigorously discussed. A review of this controversy can find no place in such a presentation as the present. We use the closed circuit method in our laboratories as the result of selection after long study of the problem. As in method, so in normal standards, two schools of practice exist.** Both take due cognizance of the variables of age and sex, but the Harris-Benedict formula (36) correlates with standing height and body weight, while the Aub-Du Bois equation (37) determines body area (calculated from the foregoing) as the third element of mutation. Again, the merits of each have been widely discussed. The practice of this laboratory is to compare the observed value with those predicted by each formula and report the mean as the probable deviation.

Before turning to the numerical data two points should be emphasized. First, all measurements are supposedly made on individuals in a basal state, i e., post-absorptive and both physically and mentally relaxed. Both methods are influenced equally by

* The methods basing the calculation of the metabolic rate on the carbon dioxide output alone are so susceptible of error as to find no place in this discussion.

** Dreyer's (35) original suggestion of the use of body weight alone, offers no advantage, and the later generalization, based on calculated weight, is inapplicable to the clinical problem through the frequent departure of the patient from the arbitrary standards implicit therein [see (12)].

failure to observe these provisions and may easily present values which are definitely misleading. As all such errors tend to raise the observed basal rate, all measurements should be regarded as maxima with the true energy requirement of the patient equal to or less than that recorded, the degree of deviation depending upon the attendant circumstances. Second, the test should be applied under standard controlled conditions and a series of supplementary physical measurements such as pulse rate, temperature, and blood pressure, should always form a part of the laboratory record. The correlation of these data with the observed rate will frequently furnish evidence of the presence of vitiating conditions which might otherwise pass unnoticed. The conventional practice to allow for individual variation is to define the normal limits as ± 10 percent from prediction. In view of the uniform tendency of error to augment the observed values we feel that -10 percent defines a definite hypofunctional trend, while equally we incline toward $+15$ percent as the preferable superior limit. In every case such conventional boundaries must never be regarded as sharply defined. In the interpretation of borderline basal rates, many concomitant observations must be taken into consideration; no single test in itself, except under most unusual conditions, is competent to establish a positive diagnosis. Its interpretation in the light of numerous other and independent records of fact lends a necessary authority not intrinsic in its own absolute magnitude. Finally, while the operation includes mechanical features, a machine-like freedom from error is far from implicit in the procedure. The sources of error are numerous and they can be held within reasonable limits only by intelligent and scrupulous care. The data for this series are given in Table XII.

With the basal metabolism data the same conventions are observed as in the presentation of the data of Table VI ("Vital Capacity"). The last three horizontal columns give the percentage distribution of the group into those above, below, and within the conventional normal limits. The presentation of the data of the other measurements does not require explanation.

Beginning with the hypofunctional group, only the gonad and adrenal cases show values above predicted levels, and in no case does the upper deviation exceed normal limits. In the case of the gonad failures, as noted earlier in the text, marked

TABLE XII
RESPIRATORY METABOLISM DATA

Observation	Endocrine														Not End.
	In Glandular Depression						In Glandular Dysfunction					In Glandular Hyperactivity			
	Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Sum.†	Pit.	Thy.	Pl. Gl.	Uncl.	Sum.†	Pit.	Thy.	Sum.†	
Basal Metabolism—															
High	−4	−10	+9	+4	−29	+9	+33	+18	+7	+18	+33	+23	+87	+87	+27*
Low	−24	−50	−25	−39	−30	−50	−28	−25	−34	−24	−34	+15	+19	+15	−22
% above prediction	0	0	8	15	0	5	11	24	21	15	18	100	100	100	48
Average	–	–	+5	+4	–	–	+8	+10	+6	+9	+8	+19	+45	+32	+7
% below prediction	100	100	92	85	100	95	89	76	79	85	82	0	0	0	52
Average	−15	−23	−13	−14	−30	−19	−12	−14	−12	−12	−13	–	–	–	−6
% above +10%	0	0	0	0	0	0	2	7	0	5	4	100	100	100	7
% between +10% and −10%	23	0	35	62	0	24	42	45	57	37	45	0	0	0	81
% = or below −10%	77	100	65	38	100	76	56	48	43	58	51	0	0	0	12
Temperature—Average	98.0	97.9	98.1	98.1	97.0	97.8	98.0	98.1	98.2	97.9	98.1	98.2	98.2	98.2	98.1
Blood Pressure, Systolic—															
Average mm	118	112	112	95	111	112	111	122	133	115	120	161	138	150	125
% =or over 150 mm	0	1	3	0	0	1	4	6	36	3	12	60	31	46	12
% = or under 110 mm	21	53	60	100	75	62	39	23	21	54	34	0	13	7	19
Diastolic—Average mm	73	72	69	53	68	67	73	74	81	69	74	92	73	83	75
% = or over 100 mm	2	1	1	0	0	1	3	6	21	0	8	40	13	27	7
% = or under 65 mm	23	28	36	100	25	42	20	20	21	35	24	20	44	32	22
Pulse—															
Average	71	69	74	75	69	72	72	77	76	74	75	81	101	91	76
% = or over 80	23	13	34	46	33	30	21	40	43	26	33	60	76	68	36
% = or unde. 70	60	58	37	38	67	52	41	23	43	43	38	20	0	10	34
Respiration—															
Average	14	15	16	15	18	16	15	16	16	16	16	13	18	16	15
% = or over 20	3	7	10	8	67	19	14	14	29	20	19	0	41	21	16
% = or under 10	10	4	8	8	0	6	8	0	14	7	5	0	12	6	12
Alveolar CO—															
Average mm	39	37	34	36	32	36	38	36	36	34	36	38	36	37	37
% over 35 mm	46	62	54	42	33	47	55	49	36	38	45	75	67	71	48
% = or under 30 mm	7	9	35	8	33	18	4	12	29	28	18	0	20	10	13

*Lymphatic Leukaemia. †Summaries are not weighted for number of cases composing each group.

nervous instability is a common feature. As we frequently have had occasion to observe, emotion, even when controlled, may cause an increase in the observed oxygen consumption which can readily assume vitiating proportions.

In the adrenal cases there is a response to fatigue which operates in the same way. As pointed out above, basal rates as observed are maxima with the true value in certain cases lying well below that recorded. Another possible explanation for the exceptions in both series may lie in our inability to define a dysfunctional state. With due cognizance of the downward trend of the energy exchange, the relative magnitudes become suggestive. Recognizing the reenforcing influence that malnutrition may exert in this group (the adrenal cases particularly), it is still apparent that the thyroid exercises the dominant influence, the pituitary and gonad the least, while the adrenal occupies a position between these extremes. The further analysis shows the adrenal to be the only member of the group in which a majority of the cases fall within the conventional limits of normality. Each of these glands will be discussed independently in later papers.

Continuing with the basal rate observations, the dysfunctional group next claims attention. Only the pituitary and thyroid of the single entities are here represented and, as could be predicted, values are found both above and below the calculated norms. The thyroid shows a series of levels produced by the intermediate transitional phases. The pituitary group includes not only such conditions but also those in which the dysfunction is caused by a difference in functional level in the two lobes. This possibility (i. e., of severe malfunction of one lobe) determines the somewhat greater scatter of the pituitary data than those of the thyroid. In the pluriglandular group one composing element is definitely hypo- (ablation) and the other dys-functional, the summation giving predominance to the downward trend. As has already been noted, in many endocrine conditions there is a distinct tendency for an initial over-active state to undergo a functional involution toward a final condition of hypoactivity. This is shown in the separation of the data given above into the three zones of over-, normal, and under-activity.

The hyperfunctional group contains but pituitary and thyroid cases. The results are clear-cut and require but little dis-

cussion. The greater influence of thyroid disease on the energy requirement is unmistakably evident. The extremes in the non-endocrine group compare favorably with the values of the dysfunctional moiety. The highest levels are recorded in cases of lymphatic leukaemia, the lowest in malnutrition. Sharp differentiation from the endocrine group comes in the zonal distribution, with 81 per cent falling inside the limits of normality. The relative rarity in this series of those non-endocrine conditions (malnutrition, nephritis with severe edema, febrile states, and leukaemias), which significantly influence the respiratory exchange determines this division.

The temperature values in the several divisions are peculiarly influenced by the undesirable feature of this method of presentation. Slight differences, therefore, are significant. In the hypo-function group, the gonad and adrenal agree with the non-endocrine average, while a downward tendency is shown by the thyroid, which is less marked in the pituitary. The pluriglandular group exhibits the addition effect of the two endocrine agencies involved. In the dysfunctional group the thyroid and pluriglandular units show an upward tendency which, in the case of the thyroid, is emphasized by the state of hyperfunction.

As to blood pressure changes, hypofunction of the pituitary causes mild, of the adrenal severe, hypotension, the thyroid and gonad groups occupy an intermediate position. It is interesting that the late cases of hypothyroidism with arteriosclerosis fail to influence significantly the general average. The dysfunctional group shows upward tendencies, with the exception of the pituitary. The dual character of the gland, with its dysfunction including possibly severe aberration in but one lobe, probably explains the seeming contradiction. The wider limits of variation shown by the basal rate support this view. In the hyperfunctional group the upward progress of the thyroid continues moderately, while the few pituitary cases assume a real hypertensive level. It is doubtful if a larger series would exhibit so marked a degree of increased blood pressure. In the present instance, one severe case could influence the average perceptibly. Actually, three of the five cases presented *hyper-* and the other two *hypo*-tension.

The pulse rates repeat the temperature relationships, with the thyroid showing the major degrees of variation. The respiration rates show a very general uniformity, only the thyroid manifesting any real increase with increasing functional activity.

Throughout the discussion on respiratory metabolism no attention has been paid to the non-endocrine group. A general normal tendency exists and the magnitudes observed are not remarkable.

Alveolar carbon dioxide is regarded primarily as an index of the combining power of the plasma. Two methods for its determination are in general clinical use, *i. e.*, that of Marriott (38), which approximates venous, and that of Fredericia (39), which more nearly expresses arterial tensions. For reasons given elsewhere (40), we prefer the latter method, and the values here recorded are all derived by it. Venous tensions would show values a few millimeters higher. The test is at best a rough one and is peculiarly susceptible to error through incooperation. Failure to expel a representative sample will inevitably lead to low values because of dilution of the alveolar air with dead or even tidal air. While all of the averages are low, only the gonad failures and the pluriglandular group in which castrates predominate show really depressed levels. The same condition obtains in pregnancy, as has been shown by the writer (40) and others, and is of potential diagnostic significance in a study like the present. Low values arising in the presence of ketosis are shown by urine examination, and a retention acidosis caused by severe nephritis is implied where the major condition has been shown to exist.

The sole remaining test of this initial group which remains to be considered is that of the sugar tolerance. For reasons discussed in detail elsewhere (41) we have selected galactose as the material for the test meal. The technique of the test has already been described. Briefly, graded doses of the sugar are administered under standard conditions, and the assimilation limit defined by the quantity necessary to produce a transitory melituria. This is, in essence, the original Hofmeister (42) technique. Blood sugar curves have been discarded (20) as relatively meaningless and lacking the essential quantitative character. The preliminary studies (43) defined 30 grams as

the tolerance dose for the normal male under all conditions, while the normal female assimilation limit varies from 20 to 40 grams, depending upon her state of sexual maturity The reasons for this intrinsic sex difference need not be discussed here; the fact is of very marked differential diagnostic value. Briefly outlined, in prepubertal years the female gives slight melituria with 20 grams; with the onset of menstruation the assimilation limit increases and usually in the course of a year reaches 40, the normal adult tolerance. This continues to the menopause, when there seems to be a tendency to regress to an intermediate level of 30 grams.*

During adult years pregnancy will cause a fall in the tolerance, first to 30 and later to 20 grams. A further fall, postpartum, is transitory, and ultimately the normal level is resumed. Menstruation itself shows a tendency to lower the tolerance slightly during the period. Removal of the ovaries restores the prepubertal level of 20 grams.

Since the normal standard for the female is variable and dependent upon the level of ovarian activity, the collective presentation of results from patients representing all of the several developmental stadia must be in relative and not absolute terms. For example, a 40-gram level represents an increase of 100 per cent above the normal for the prepubertal child and is the exact normal level for the healthy woman of thirty years in a state of sexual rest. By reporting the deviation of the individuals from their personal norm in terms of per cent, data are secured which are comparable to each other. In presenting the results of this test (*i. e.*, percentage deviation from the norm), this convention has been adopted. While the male standard remains unchanged through life, the same convention has been followed for the sake of uniformity. In discussing the results obtained, it may not be out of place to repeat that as they are derived from individuals showing wide degrees of variation in functional level, the average values are much less than the deviation shown by individual cases in the series. Mild and severe conditions, with the several intermediate gradations, manifest themselves quantitatively through the amount of their variations from the standard. The

* The differences are undoubtedly gradual and progressive. In applying the test, it has been found to be practical to vary the several test doses by 10-gram amounts, and this convention defines the figures as given.

method of averages lessens the apparent magnitudes, leaving the expressed tendencies significant in sense and degree. In tests of this character the dysfunctional group, which is made up of mutually compensating units, tends toward a misleading normality. In the effort to minimize these hampering conditions as far as possible presentation is made with the same detail as that employed in the preceding table. The galactose tolerance data are given in Table XIII.

NOTES

A. A few cases have been omitted from the tabulation as a concomitant non-endocrine disease influencing sugar tolerance makes them mask the true picture.
   1. One hypothyroid patient (male) at 60 gms. had an advanced chronic intestitial nephritis, and one at 20 gms a demonstrated liver involvement.
   2. Four hypothyroid patients (female) with demonstrated liver disorder average —68%.
   3. Two male castrates at 40 gms. had late chronic interstitial nephritis.
   4. Four hypogonad patients (female), averaging —80%, had severally cases of central nervous lesions (2), syphilis (1), and liver disorder (1).
   5. Three hypogonad patients (female), showing a normal postmenopause tolerance of 30 gms., all had an established nephritis and were over 60 years old.
   6. One hypoadrenal patient (female), with raised tolerance (+25%), had a long established chronic interstitial nephritis.

B. In the pluriglandular cases, 20 gms. is taken as the demonstrated normal tolerance for the castrated female.

In the hypofunctional group failure of the pituitary uniformly produces an increase in tolerance of very marked proportions. With failure of the thyroid the same direction is observed, but both the amount of the increase and the frequency of its appearance fall far short of the pituitary influence. With the testicular failure no change is observed, while with the hypoovarian patients there is uniformly a depression of the tolerance which in the average falls just short of 50 per cent. It is to be remembered that the group herein reported, however, contains only females in whom the menstrual function had been established; in the other words, with sugar tolerances above the prepubertal level. Hypoadrenalism, like gonad failure, seemingly causes a downward tendency and one of even more definite proportions than in the ovarian cases. This observation is at variance with all other reports recorded in the literature and has already been noted in connection with the exhibition of glycosuria

TABLE XIII

GALACTOSE TOLERANCE

Observation		Endocrine										Not End.
		Hypo-functional					Dys-functional				Hyper-functional	
		Pit.	Thy.	Gon.	Adr.	Pl. Gl.	Pit.	Thy.	Pl. Gl.	Uncl.	Pit.	
Male—	High(gms.)	70	40	30	30	–	50	30	–	30	20	40
	Low (gms.)	40	30	30	20	–	5	20	–	10	5	10
	% above normal	100	14	0	0	–	4	0	–	0	0	5
	% dose variation above normal (Av.)	+73	+33	–	–	–	+50	–	–	–	–	+33
	% =normal	0	86	100	67	–	12	33	–	33	0	41
	% below normal	0	0	0	33	–	84	67	–	67	100	54
	% dose variation below normal (Av.)	–	–	–	−33	–	−50	−33	–	−50	−53	−40
Female—	High (gms.)	120	60	30	40	50	80	40	60	40	20	40
	Low (gms.)	40	30	20	5	20	5	20	5	20	20	5
	% above normal	100	38	0	0	50	7	0	15	0	0	0
	% dose variation above normal (Av.)	+72	+29	–	–	+100	+85	–	+75	–	–	–
	% =normal	0	62	0	17	25	1	70	15	11	0	42
	% below normal	0	0	100	83	25	92	30	70	89	100	58
	%dose variation below normal (Av.)	–	–	−45	−52	−25	−52	−25	− 6	−35	−50	−39
	Summary											
% above normal		100	32	0	0	50	6	0	15	0	0	2
% =normal		0	68	*100	33	25	5	56	15	17	0	41
% below normal		0	0	†100	67	25	89	44	70	83	100	57

* Male. † Female.

in some of these cases. The fact only is recorded here and will be discussed more appropriately in a later paper. The pluriglandular cases exhibit the result of summation of the several diverse agents comprehended in the group.

The data in the dysfunctional group include only the pituitary, thyroid, and the pluriglandular cases. The transition influence is manifested with the pituitary, a few of the cases having been examined at a time when they were passing through the zone of normality. A persistence of an earlier overactivity is shown by the thyroid group with 44 per cent of the cases exhibiting a lowered tolerance. In the pluriglandular group the ovarian element is more in evidence than in the hypofunctional fraction in which pituitary failure dominated the series.

It is to be regretted that hyperthyroid cases do not appear in this summary. As was stated earlier, this condition does not ordinarily require so elaborate an investigation for the establishment of a diagnosis. The sugar test requires three days, and when a diagnosis could be made by a morning's study, co-operation was not obtainable for this time-consuming addition. Since this series was completed a few hyperthyroid cases have been given the sugar test. They confirm, in the main, the inference to be drawn from the two groups here presented, namely, a moderate lowering of the tolerance. Lowered tolerance with cases showing overactivity is seemingly of more frequent occurrence than is the converse in thyroid failure. A warrantable inference from this fact would be of the possible production by the thyroid of a second hormone acting on carbohydrate metabolism as thyroxin—or something related to it—may be regarded as regulating the energy metabolism. The hyperpituitary cases exhibit a strait antithesis of those showing failure. The practical abolition of any tolerance for galactose is the common finding in severe cases of overfunction.

A word in passing may be offered on the frequent association in the literature of pituitary disease with diabetes. That it is in some measure an outgrowth of the untrammeled speculations of the Viennese school admits no doubt, but it is perpetrated by several writers who patently do not subscribe to the theory of an interlocking glandular directorate. If the lowered tolerance of the acromegalic is but an expression of direct inhibition of the function of the islands of Langerhans, then consistently,

in hypofunction of the former the increased sugar tolerance must signify an augmented production of insulin or lessened inhibition of its activity. In one of our cases, not reported in this series, the galactose tolerance was 300 per cent above the normal. This should imply at least an equal increase in available insulin, the sequel of which would but ill accord with the typical pituitary obesity and the normal blood sugars. Many other arguments are adducible, but they may be left more fittingly, to later discussion. That influence on carbohydrate metabolism is not confined to the endocrine group is apparent from the table. Lowered tolerances predominate—the few high values being seen in advanced nephritis. In the group characterized by a lessened power of assimilation are found cases presenting various lesions of the central nervous system, syphilis, primary anaemia, liver disorders, malignant neoplasm, and psychoneuroses. The wisdom of excluding such fairly frequent disease conditions before interpreting a sugar test in terms of endocrine disorder should not require comment.

Before leaving this portion of the work, certain correlations may prove of value. In presenting them not only will the summaries already presented be considered, but, equally, individual cases representing extreme conditions. These latter must take first place, as in them one finds the extreme limits defined, and hence the functional tendencies illustrated most clearly. Equally, it must be borne in mind that in selecting the extreme case many features may present that in early and intermediate states do not occur in really significant magnitude. Such presentation, therefore, must be used with due caution when applied to the individual case.

TABLE XIV

PHYSICAL MEASUREMENTS

Influence of Hypofunction

	Pituitary	Thyroid	Gonad	Adrenal
Height	— — —	— — —	(+ +)	?
Sitting Height Index	— —	+ +	— —	?
Weight	+ + +	+ +	+ +	—
Lung Volume	—	— — —	—	—

To allow compact form, the data will be reduced to tables. In the interest of simplicity only hypofunctional tendencies will be listed, as the known and established hyperfunctional condi-

tions present in the main antitheses to the former. Dysfunctional states present too many permutations of the extreme types to be easily presentable. Records from the literature, not observed in this series, are enclosed in brackets.

Pituitary and thyroid dwarfism are coupled with the overgrowth of the long bones said to occur from castration in childhood (males only). A clear-cut adrenal influence has not been defined. The values for the sitting height index are probable but not certain. The weight relation seems fairly well established and that of the lung volume definitely so.

The urine values are insusceptible to this form of analysis. The urines in pituitary and gonad cases tend toward the normal, those with thyroid disease simulate, and those with adrenal malfunction define the picture of nephritis. This adrenal tendency is well marked in the urea curve. In the nitrogen partition the thyroid and adrenal cases show the greatest tendency toward high residual fractions and absolutely high values as well. The pituitary influence is indeterminate, the gonad picture tends toward normal.

The high blood uric acid of the pituitary cases, and high residual nitrogen and low blood sugar of adrenal disease, are the outstanding features of this group of analyses.

The general low white count and lymphocytosis, the latter most marked in adrenal, though frequently assuming high values in thyroid cases, and the eosinophilia of the pituitary and adrenal cases, are the most salient features of the blood morphology.

The accessory physical measurements incident to the respiratory metabolism may be presented in tabular form.

TABLE XV

PHYSICAL FUNCTION

Influence of Hypofunction

Datum	Pituitary	Thyroid	Gonad*	Adrenal
Temperature	—	— —	0	0
Pulse	—	— — —	0 or +	0
Respiration	0	— —	0 or +	0
Blood Pressure	—	— —	— —	— — —
Alveolar CO_2	0	0 or —	— — —	0 or —

* Ovary only. The loss of the testicles in adult years lowers blood pressure and pulse rate slightly, but seemingly does not produce any marked effect in man.

The average pituitary case shows a generally normal trend, the thyroid a depression varying only in amount, ovarian failure produces a marked drop in blood pressure and a unique depression of alveolar carbon dioxide, while hypofunction of the adrenal exhibits a significant departure from normal only in its extremely low blood pressures.

As a point of differential significance the joint consideration of basal rate and sugar tolerance shows both qualitative and quantitative relations which are highly informative.

TABLE XVI

COMPARISON OF OXYGEN AND CARBOHYDRATE METABOLISM

Influence of Hypofunction

Datum	Pituitary	Thyroid	Gonad	Adrenal
Basal Rate.....	—	— — —	—	— —
Galactose Tolerance.	+ + +	+	— —	— — —

Of the gonads only the ovary again is considered. Ablation of the testicles in adult years produces but a slight drop in the basal rate and no change in sugar tolerance. The differential features of the above scarcely require comment. One condition is frequently met that cannot be resolved by the above relationship. Many women are seen who show a basal rate of from —15 per cent to —20 per cent, and a sugar tolerance of 20 grams. These data could be due either to primary hypogonadism or to the common type of pituitary dysfunction with the anterior lobe under-, and the posterior, over-active. The remainder of the laboratory and clinical picture is absolutely essential to resolve the problem, the initial outcome many times being to establish no more than a greater probability for one or the other diagnosis.

With the foregoing expository statement concerning those tests whose character permits in some measure this form of presentation, attention may next be given to the group of special examinations.

In the main, these are chiefly serviceable as indicating the presence or absence of a non-endocrine disease state to which both the patient's presenting symptoms, as well as the results of certain of the laboratory tests, might be attributable. Exceptionally, such examinations may give positive evidences of endocrine significance, and to these the following discussion will be

limited. Before taking up details, however, a brief review of the extent of the special examinations may be presented in tabular form.

TABLE XVII

SPECIAL EXAMINATIONS

Examination	Cases Examined	Positive Findings No.	%
Eye	596	460	87
Ear	206	60	29
Barany	100	25	25
Audiogram	121	111	92
Nose and Throat	40	23	58
Heart (1)	26	14	54
Pelvic	161	54	34
Cystoscopic	14	7	50
Orthopedic	13	12	92
Neurological	310	169	55
Skin	20	20	100
Endermal	47	25	53
Biopsy	6	4	67
Sputum	15	3	20
Duodenal Function	8	3	38
X-Ray (General) (2)	633	362	58
X-Ray (G. I. Series) (3)	30	14	47
Miscellaneous	240	..	..
Total	2586		

(1) An electrocardiograph was not available at the time this series was completed.

(2) Each of these cases had a series of x-ray plates. Pictures of sella, sinuses, and thyroid were always secured and frequently chest, measured heart, and other plates were added.

(3) The Graham test had not been described at the time this series was completed.

It will be seen from the above tabulation that the average of special examinations for each case falls between 2 and 3. Since this series was completed additions to the staff, together with increase in equipment and inclusion of new methods, has augmented this phase of the work. At the present time the long

form cases average 8+ and the short form studies 5+ consultations.

The special examinations yielding positive information as to endocrine status may be taken up seriatim.

1. *Liver Function:* These studies—and more significantly the later investigations which have profited greatly through the application of new methods, the products of this and other research institutions—have demonstrated a frequent incidence of liver dysfunction in thyroid failure. There is not necessarily an earlier history of icterus nor of symptoms pointing to liver or gall bladder disease. The Graham test (44), icteric index (45), van den Bergh reactions (46), and more especially the elaborate methods based upon the examination of the duodenal contents which have been devised by McClure (47), give many channels of approach for the resolution of this problem. Such a liver condition may mask the otherwise clear-cut evidences of thyroid disease (modified sugar tolerance, atypical blood picture), and render a diagnosis uncertain. The condition is usually functional in character and frequently yields to duodenal lavage. Migraine of hepatic origin is frequently a concomitant picture.

2. *Ophthalmological Examination:* The production of ocular disturbance by pituitary tumors has been frequently recorded [Josefson (48), Cushing and Walker (49), de Schweinitz (50)], and even through temporary enlargements, as in pregnancy [Erdheim and Stumme (51), Carvill (52)]. Others have recorded changes even when no tumor growth could be demonstrated, and Oppenheim (53) has suggested the existence of a circulating toxic substance derived from the gland and producing optic nerve degeneration. As reported by Rowland (54), a yellow color of the discs, enlarged blind spots, and contraction of the form and color fields are frequently observed in pituitary disease in the absence of demonstrable tumor growth. One or more of these phenomena may also be found in thyroid and gonad involvements, though with less frequency than in the pituitary cases. That the general metabolic disturbance is a direct causal element is seemingly capable of demonstration. The pituitary, from its anatomical relationships, exercises influence through two channels, the others presumably through but one. Other

manifestations, such as cutting of the upper form fields and marked concentric contraction of the form and color fields have been recorded and are shortly to be discussed in the literature. Besides the direct endocrine indications, many evidences of non-endocrine disorders may be elicited in thorough eye examinations. In skilled hands the eye examination is probably more generally suggestive and informative than any other one special examination both in endocrine disease and in other non-endocrine localized or general derangements.

3. *Electrocardiogram:* It has been shown by Thacher and White (55) that thyroid failure may produce a more or less characteristic electrocardiographic picture; these findings have in part been substantiated in our clinic.* An interesting feature is the restoration of the picture to the normal under thyroid medication (see later paper on the thyroid).

4. *X-Ray:* Aside from the large amount of information concerning non-endocrine conditions which this form of examination offers, there are potentially certain direct evidences which should be expected. Lack of epiphyseal union or premature closure are instructive and may support other evidences of aberrant growth relations of endocrine origin. Substernal thyroids may be shown by this means, and the information is of supplementary value.

Sella pictures are of value only when actual erosion of the clinoids or floor has taken place as the result of pronounced hyperplasia. In the great majority of pituitary cases, however, a normal sella is seen—if such a term be warranted to describe a bony structure so variable in its formation [see Camp (56)].

Equally, the diversity of outline of sellae enclosing wholly normal glands suggests caution in the establishment of a pituitary diagnosis on the evidence of a possible abnormal configuration of this structure alone. Thymus shadows, while possibly informative, lack specific indication. Aside from the lack of evidence of a true endocrine function of this gland, certainly in adult years, so-called persistent thymi are found to be far more frequent in necropsy reports than certain clinical writings would seem to indicate. They have been frequently observed in indi-

* Reid. Unpublished data. Personal communication.

viduals of adult and advanced years who have shown no other evidence of a status thymico-lymphaticus.* It would seem equally plausible to regard a persistent thymus, in some cases at least, as but one evidence of a growth anomaly incident to an established endocrinopathy known to influence development. Further, it may be regarded as a resultant element in status lymphaticus rather than the causal factor.

One other finding under this caption requires brief comment. The inclusion of the pineal in the endocrine group is still open to question. Dandy's experiments (57) fail to show any real endocrine influence. Parenthetically it may be said that complete extirpation experiments that yield negative results are by far the most decisive; positive evidences may be produced by trauma to adjacent parts or to other agencies unassociated with the primary object of the experiment. In this series, 29 cases were reported with x-ray shadows interpreted as calcified pineal glands. The etiological classifications gave:

Not Endocrine	9
Pituitary Dysfunction	14
Pituitary Hypofunction	3
Gonad	2
Unclassified	1

In none of these cases was there demonstrable any stigmata which could be associated with the conventional evidences of pineal disease, nor did any of the histories contain suggestive records. It may be argued that all of the subjects were adults and that the pineal condition had probably occurred only after maturation. Such a position is tenable but equally if adopted leads to the inevitable corollary that in adult years, at least, the pineal has no striking endocrine function. While pituitary cases constitute over one-half of the group, it must remembered that there were 270 of them who showed no pineal shadows—and that, further, many of the other patients did not have x-rays of the skull.

5. Such endocrine data as may be elicited by neurological, pelvic, and skin examinations are too well known to require elaboration in this report.

* Personal communication from Dr. George Burgess Magrath.

The many other observations listed are primarily important, as was stated above, in defining concrete disease conditions unassociated with the endocrine glands.

A few additional words may be permitted before bringing this first paper to its conclusion. The author wishes to emphasize that this can be at most but a preliminary communication. He may say with perfect candor that he is as acutely aware of the many shortcomings of this work as can be any of his readers. That it is the first formal presentation of investigations begun in 1912 is an earnest of good faith. What it embodies may be briefly stated. Certain objective criteria have been established for the determination of the presence of endocrine disease, and, further, its allocation to the individual gland at fault. Equally, it has been shown that a variety of non-endocrine conditions may simulate endocrine diseases both in some of their many clinical aspects, and equally in certain of the significant laboratory findings. In other words, for the establishment of the true etiology it is essential to conduct a general diagnostic study with the possible endocrine element determined only by exclusion. We have applied the method to the study of nearly 3,000 cases with results that seem to us encouraging, even while we recognize the limited amount of real knowledge yet available and the vast extent of the territories still unexplored. It is our hope that application of the correlations here presented may prove of some service to our colleagues in the resolution of their own problems. This independent application is essential to establish such worth as may lie in this method of approach.

Effort has been made to avoid controversy. Where the findings are at variance with conventional endocrine doctrine, the observed and tested facts upon which the conclusions rest are offered to speak for themselves. Many points of first importance must still be largely matters of interpretation, but at least objective data offer a firm foundation for a common starting point.

In conclusion, the writer wishes to pay his heartfelt tribute of thanks and appreciation to the many who have participated in this work. In the first place, thanks are due to those volunteers in the early days whose willing co-operation made the establishment of the normal standards possible; an even greater measure of appreciation is offered to those who in suffering and with disease heavy upon them gave a gracious and willing aid that

others might profit where they could not. Every tribute must be paid to the laboratory staff of the Evans Memorial, by whose skilled and patient hands the tens of thousands of exacting and delicate operations have been performed with consistent accuracy. And finally, a basic indebtedness is acknowledged to the group of friends, colleagues, and fellow workers, the full staff of the institution, whose generous assistance, highly skilled service and unfailing support and encouragement have made this work possible.

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EXOPHTHALMIC GOITER AND MYXEDEMA: REPORT OF A CASE*

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The characteristic phenomena of exophthalmic goiter are probably brought about because of the production and delivery to the tissues of an abnormal agent from the thyroid gland. This agent is usually associated with an excess of the normal thyroid secretion, but that it must be so is not essential to the hypothesis that in exophthalmic goiter two products are elaborated by the thyroid gland, nor is it consistent with theoretical or practical considerations of thyroid function and disease. There is abundant evidence that the thyroid gland may produce amounts of secretion sufficient to hold the basal metabolic rate at a normal level and still be associated with the phenomena of exophthalmic goiter, presumably because of an abnormal secretion. It is theoretically possible to have the abnormal thyroid secretion so limited in amount that, when controlled with compound solution of iodine (Lugol's solution) the patient shows frank evidence of myxedema; and in the same patient to find the phenomena of exophthalmic goiter when the patient is not taking iodine. This condition is exemplified in the following case:

A woman, aged twenty-eight, registered at the Mayo Clinic, September 13, 1924, complaining of protrusion of the right eye. Sixteen months previously she had become tired, nervous, and had lost 30 pounds in two months, in spite of a normal diet. Tonsillectomy was performed at that time, and following this she had gained strength and weight; the right eye, however, had become prominent. The nervousness disappeared and during the year before admission she had been intolerant of cold, had tired easily, and lacked energy.

General examination disclosed dry skin and moderate exophthalmos of the right eye. The thyroid gland was just pal-

* This case has been referred to by H. S. Plummer: The function of the thyroid gland. In the Beaumont Foundation Lectures, St. Louis, C. B. Mosby Company, 1926, 45-82.

pable. Measurement of the eyes with the exophthalmometer showed the right to be 20 mm., and the left 18 mm. The basal metabolic rates were —13 and —16 per cent. It was thought that the patient had had exophthalmic goiter with residual exophthalmos, and that the present symptoms were the result of a mild degree of hypothyroidism, or that the patient was one of those persons who normally have a low basal metabolic rate. The basal metabolic rate was elevated, and the patient was sent home with instructions to take 2 grains of desiccated thyroid daily, a dose which was holding the basal metabolic rate at —4 per cent.

January 25, 1924, the patient returned. For the previous two weeks there had been loss of strength, increased sweating, and palpitation. She had lost 15 pounds in weight. The exophthalmos had remained unchanged, but stare was present. The right lobe of the thyroid measured 2 by 5 cm. and was very hard. There was frank evidence of hyperthyroidism. The basal metabolic rates were +49 and +52 per cent. The desiccated thyroid was discontinued, but there was no change in the basal metabolic rate after nine days. A diagnosis of exophthalmic goiter was made. The patient was then given ten drops of compound solution of iodine three times daily and in ten days the basal metabolic rate had dropped to +30 per cent, the stare had disappeared, and the patient was improved. March 3, partial thyroidectomy was performed, leaving thyroid tissue amounting to half of the normal lobe on each side. The tissue removed weighed 62 gm. and the pathologic report was "hypertrophic parenchymatous thyroid." March 13, 1924, the patient felt well; the basal metabolic rate was +1 per cent.

At the first observation there was no clinical evidence of myxedema; however, it is to be noted that the basal metabolic rate at that time was —16 per cent and the edema of myxedema does not usually appear until the basal metabolic rate has dropped to —18 or —20 per cent. In view of the condition of the patient at the time of the second admission it was assumed that she had first come to the clinic in a state of complete remission from exophthalmic goiter. She was apparently a person whose basal metabolic rate is lower than the average normal. Exopthalmic goiter often develops in this type of case.

March 4, 1925, she returned for examination. She had been

in normal health until July, 1924, when she had again become nervous, had palpitation, and exophthalmos appeared in the left eye; that in the right eye had increased somewhat. In January, 1925, she had taken compound solution of iodine and had noted little change, except that there had been considerable intolerance to cold. At the present examination, moderate exophthalmos of both eyes was present, and there was edema of the lids of both eyes. The skin was cold. The facies was typically that of myxedema and there was bilateral exophthalmos. The basal metabolic rates were —28 and —30 per cent.

From the history it was clear that five months following thyroidectomy there had been a recurrence of exophthalmic goiter. This had been controlled with the iodine, and later the thyroid remnant had produced an insufficient quantity of its secretion to hold the basal metabolic rate at normal. It was anticipated at the time of this admission that stopping the iodine would allow the basal metabolic rate to rise and the characteristic evidences of exophthalmic goiter to appear. This opinion was based on Plummer's hypothesis that in exophthalmic goiter there is an active agent produced by the thyroid gland which causes the characteristic phenomena of this disease, and which is, presumably, an abnormal form of thyroxin. This abnormal agent is usually, but not necessarily, associated with excessive secretion of normal thyroxin. If, in this case, the phenomena of myxedema could be produced at will by the administration of iodine and by stopping it, these phenomena could be made to disappear and evidence of exophthalmic goiter substituted, we would then have proof of the coincident existence in this patient of both myxedema and exophthalmic goiter. Furthermore, almost incontrovertible evidence would be established in support of this hypothesis.

Compound solution of iodine, which had been taken continuously since January, was stopped and the basal metabolic rate rose, after sixteen days, to —14 per cent. The patient then complained of nervousness; the intolerance to cold had disappeared. Edema of the eyelids diminished, and stare characteristic of exophthalmic goiter was present. Compound solution of iodine was again given and after eighteen days the basal metabolic rate had again dropped to —25 per cent, with reappearance of the evidence of myxedema and loss of the stare and

nervous manifestations. Iodine was continued and desiccated thyroid was given; the basal metabolic rate rose to —2 per cent. Evidence of myxedema disappeared and there was considerable improvement in the patient's symptoms.

In October, 1925, the patient returned. At this time she felt better than at any time since the onset of the illness. The exophthalmos had diminished and there was no edema of the lids. The basal metabolic rates were —7 and —6 per cent; the iodine was stopped and the desiccated thyroid continued in the same dosage. The basal metabolic rate rose in fourteen days to +6 per cent, the patient became nervous and warmer, the eyes stared and puffiness of the lids of the type seen in exophthalmic goiter appeared. She was dismissed with instructions to take both compound solution of iodine and desiccated thyroid. A letter written October 7, 1926, stated that she had stopped all medication in February, 1926. The protrusion of the eyes remained the same. Since this time, she had noticed a slow pulse, and marked intolerance of cold. There were no nervous symptoms.

The response to iodine was exactly as anticipated, and, as is seen, relief from symptoms came only from the simultaneous administration of iodine and desiccated thyroid. There was, then, absolute deficiency of the thyroid secretion, and what secretion was present was partially of the character of that produced in exophthalmic goiter. Obviously, then, the cause of exophthalmic goiter was still active in the patient for some time following thyroidectomy, although when the abnormal agent of this disease was brought under control by compound solution of iodine, she became myxedematous. From the later correspondence it is apparent that the cause of exophthalmic goiter has since ceased to be active, but the thyroid deficiency persisted. Several cases have been seen in the clinic presenting the syndrome of exophthalmic goiter, and with basal metabolic rates from 0 to ±10 per cent, dropping from —5 to —15 per cent after the administration of iodine. This case, however, is the only one observed in the clinic in which the basal metabolic rate was depressed because of the administration of iodine to so low a level as to be consistent, and coincident with the characteristic frank manifestations of myxedema.

EPINEPHRINE SENSITIVENESS AT THE MENOPAUSE

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In a monograph recently published by myself (1), dealing with the causation and treatment of "flushing" at the menopause, and in a paper published in the British Medical Journal (2), I have drawn attention to certain phenomena associated with the administration of epinephrine to women at the menopause who complained of flushing. These were:

FLUSHING PRODUCED BY EPINEPHRINE

Intravenous injections of 10 minims of a 1 in 1,000 solution of epinephrine hydrochloride in women complaining of flushing at the menopause gave rise, in all instances, to an immediate attack of flushing which was, in all respects, identical with those attacks which occurred spontaneously.

A consideration of the results obtained by observers, such as Petzetakis, on the effects of intravenous injections of epinephrine in normal individuals, yields no evidence of the production of flushing by this substance in such individuals. Control injections were given to my patients of the extract of the posterior portion of the pituitary body and of normal saline; no flushing, however, was produced by these injections.

Goetsch has shown that in some cases of hyperthyroidism the patients are remarkably sensitive to injections of ephinephrine, and attacks of flushing have been frequently observed following the administration of epinephrine to such individuals.

Basal metabolic investigations were not performed in my cases, but no clinical signs of hyperthyroidism were present; furthermore, only those women were utilized for experimental work whose weight had remained constant or had increased since the onset of the menopause.

EPINEPHRINE MYDRIASIS AT THE MENOPAUSE

Dixon has shown that instillation of epinephrine into the

conjunctival sac in normal individuals does not give rise to dilatation of the pupil.

Forty per cent of those women at the menopause complaining of severe flushing, whom I subjected to this test, showed dilatation of the pupil of transitory duration. The reaction was found to be constant on eight consecutive days in each instance.

Loewi has stated that epinephrine mydriasis may occur in cases of pancreatic diabetes. Bearing this in mind, therefore, an examination of the urine was undertaken where the pupil reaction to epinephrine occurred; in no instance, however, was evidence of glycosuria obtainable.

Since publishing these findings, I have extended my researches as follows:

INTRAVENOUS INJECTIONS OF EPINEPHRINE IN WOMEN AT THE MENOPAUSE NOT COMPLAINING OF FLUSHING

As was the position in my original experiments, the difficulty in obtaining clinical material was considerable. It was necessary to obtain patients who, after being fully informed of the unpleasant symptoms and the possible risk associated with the intravenous injection of epinephrine, were still willing to cooperate in the investigation required. Three volunteers only were forthcoming, and in these women I gave intravenous injections of 10 minims of epinephrine hydrochloride, diluted in 10 cc. normal saline. The injection was given extremely slowly. Immediately the injection was concluded, the pulse rate was found to be increased and the arterial tension raised (to the palpating finger).

With this increase in tension and pulse rate there occurred palpitation, headache, distress, and pallor of the face. This stage lasted between four and five minutes, and was identical with that which occurred following the intravenous injection of epinephrine in women at the menopause who complained of flushing. In the next stage, the headache and palpitation disappeared; the pulse rate fell to below normal level and was of low tension; some faintness was complained of. This stage, which I call the stage of reaction, lasted between four and five minutes. On comparing this stage with the one produced in those women at the menopause complaining of flushing, it would

seem that the stages in each group are identical with one exception; namely, the production of flushing. In other words, intravenous injections of epinephrine in women at the menopause produce flushing in the reactionary stage where this symptom has been complained of prior to the injection, and do not produce flushing where the menopause is not naturally associated with this symptom. In both groups the stage of reaction was quickly followed by a return of both the pulse rate and blood pressure to the normal level and the disappearance of all symptoms associated with the injection.

SUBCUTANEOUS INJECTIONS OF EPINEPHRINE

(a) *The Menopause associated with flushing*

A series of subcutaneous injections of .5 cc. epinephrine hydrochloride was given to 10 women at the menopause complaining of severe flushing; 10 women at the menopause not complaining of flushing, and 10 women having regular menstrual cycles.

The systolic blood-pressure and pulse rate were observed at five-minute intervals for 30 minutes. Subjective and objective symptoms were carefully noted and the conditions at the site of the injection closely observed. The maximum rise noted was coincident in time for both the blood-pressure and the pulse rate, and occurred in five minutes, 1 instance; in ten minutes, 6 instances; in fifteen minutes, 2 instances, and in twenty minutes, 1 instance.

The maximum increase in the systolic blood-pressure noted, in this series, was 25 mm. Hg.; the minimum, 12 mm. Hg. With the increase in blood-pressure there occurred an increase in the pulse rate of between 7 and 18 beats per minute. In all instances the blood-pressure and pulse rate had returned to the normal level within 30 minutes after giving the injection of epinephrine.

Palpitation was complained of by 6 women; throbbing in the head by 2, and 4 did not complain of any abnormal sensation. No flushing was observed in any instance.

In no case in this series were signs of hyperthyroidism present.

(b) *Menopause without flushing*

No change in the systolic blood-pressure or pulse rate above

5 mm. Hg., and 7 beats per minute, respectively, was observed; nor were there any subjective or objective disturbances associated with the injections in this series.

In 2 of the 10 women in this group increased sensitiveness to subcutaneous injections of epinephrine had been observed some weeks previously. Both of these patients had, at the time of the epinephrine sensitiveness, attacks of flushings; no increased sensitiveness was, however, observed on the occasion of these experiments when the flushings were not present.

(c) *Women with normal menstrual cycles*

No rise in the systolic blood-pressure or increase in the pulse rate above 8 mm. Hg., and 5 beats per minute, respectively, was noted in these women; subjective and objective symptoms were absent. The site of the injection showed, in all three groups, intense vaso-constriction immediately following the administration of epinephrine, which was still present, in lessened degree, at the end of 30 minutes.

FURTHER OBSERVATIONS ON EPINEPHRINE MYDRIASIS AT THE MENOPAUSE

Technique: Two drops of epinephrine hydrochloride were instilled into the conjunctival sac at 5-minute intervals, for 20 minutes. The reaction was considered to be positive if the pupil became obviously dilated, when compared with the untreated eye, within this time.

My material consisted of 32 women at the menopause complaining of flushing of varying intensity; 21 women at the menopause not complaining of flushing; 40 women with normal menstrual cycles.

(a) *Women at the Menopause complaining of flushing*

Of the thirty-two women in this group, only 2 gave pupil dilatation—namely, 6.2 per cent. In both of these patients, as in my original series, the mydriasis was noticeable 5 minutes after the instillation. The duration of the dilatation was 2 minutes in one instance, 3½ minutes in the other.

The urine was tested for glycosuria in both of these women. It will be noticed that, in this group, only 6.2 per cent gave an

epinephrine mydriatic reaction, as compared with 40 per cent in my original series.

It will be remembered that my original series consisted only of women suffering from severe flushing, whereas the group under consideration consists of women suffering from flushing of varying intensity. Furthermore, the 2 women in my latest series who gave an epinephrine mydriatic reaction, both complained of severe flushing. It would seem, therefore, that the intensity of the flushings has much to do with the incidence of epinephrine mydriasis at the menopause.

(b) *Women at the menopause not complaining of flushing*

No mydriasis was observed in this group.

Of the 21 women in this series, 5 had previously shown epinephrine mydriasis.

The positive pupil reaction was associated with attacks of flushing which had completely ceased at the time of the present experiment.

(c) *Women with normal menstrual cycles*

No mydriasis was observed in this series.

A consideration of these results justifies, I think, the following conclusions:

1. Women at the menopause who complain of flushing show an increased sensitiveness to epinephrine.
2. This increased sensitiveness is manifested as certain atypical phenomena associated with:
   (a) Intravenous injections of epinephrine.
   (b) Subcutaneous injections of epinephrine.
   (c) Instillation of ephinephrine into the conjunctional sac.
3. Whereas the atypical phenomena associated with the intravenous and subcutaneous injections of epinephrine are present in all cases of the menopause associated with flushing, epinephrine mydriasis is present only in cases complaining of severe flushing.
4. The atypical epinephrine phenomena do not occur in:
   (a) Those women at the menopause who do not complain of flushing.

(b) Women whose menstrual cycles are normal.

5. Epinephrine sensitiveness at the menopause associated with flushing disappears when the attacks of flushing cease.

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THYROXIN AS A DEPRESSANT OF CELL DIVISION; ITS EFFECT ON THE CLEAVAGE AND EARLY DEVELOPMENT OF SEA URCHIN AND ASCIDIAN*

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Of the many studies of thyroid function that have appeared in recent years, relatively few have been concerned with the part played by the thyroid in differentiation. Fewer still have contributed observations on the influence of the thyroid on cell division. And among the latter, evidence of a direct effect on the dividing cell is almost entirely lacking.

Champy (1) described marked accelerations of cell division in certain regions of the frog tadpole following the addition of total thyroid to the aquarium water. Horning and Torrey (2, 3) found that the barbule cells of the laced feathers characteristic of male domestic fowls are increased in number and their division accelerated by the addition of desiccated thyroid to the daily ration or the injection of thyroxin into the peritoneal cavity. In neither of these cases, however, is the effect due demonstrably to the direct action of the thyroid hormone on the cells concerned, uncomplicated by contributions from other tissues.

Ebeling (4) avoided such difficulties for the most part when he added living thyroid epithelium to pure cultures of chick fibroblasts and saw that the latter divided more rapidly than the controls. Carrel (5) had already found that the application of thyroid pulp to cutaneous wounds of the dog augmented the rate of cicatrization. But he found also that extracts of various tissues, of the Rous sarcoma, and of whole embryos, produced similar accelerations of the growth of connective tissue *in vitro;* and that no acceleration was produced by extracts that had been heated to 70 degrees or had been filtered through a Chamberland filter. Eberling's results, therefore,

*The observations recorded here were made at the Tortugas Laboratory of the Carnegie Institution of Washington, whose guest I was and for whose hospitality I am greatly indebted.

do not identify the activating substance or substances derived from the thyroid cells with the thyroid hormone; nor does Ebeling make any such assumption.

In sharp contrast with these effects of total thyroid when given to intact organisms or added to tissue cultures is the *depressing* effect which the crystalline thyroxin obtained from the thyroid has been observed to exert on the division rate of *Paramecium,* the magnitude of the effect varying with the concentration of thyroxin in the culture medium [Riddle and Torrey (6), Torrey (7); Torrey, Riddle and Brodie (8)]. Cori (9) concluded that thyroxin accelerates the division rate of *Paramecium,* though to a much smaller degree than thyroid extract. Woodruff and Swingle (10) were convinced by their experiments that "neither thyroxin (Squibb's) nor commercial desiccated thyroid, or fresh desiccated thyroid of the turtle produce any significant acceleration of the division rate of *Paramecium.*" With this conclusion our own observations are in entire accord.

With thyroxin it is possible to obtain various reactions associated with thyroid activity and at the same time avoid some of the difficulties entailed by the use of the latter. By exposing protozoans like *Paramecium* to solutions of thyroxin, it is possible to bring the latter into direct contact with single cells, under conditions permitting direct observation. The bacteria forming the essential food supply of *Paramecium* introduce a source of error. This, we believe, was successfully controlled in our experiments. But was the reaction of *Paramecium* a special case?

To test this question, evidence has been sought in two directions, namely, from tissue cultures—modifying Ebeling's experiment by substituting thyroxin for living thyroid epithelium —and from the cleavage stages of suitable eggs. Preliminary results obtained by my assistant, Miss Hope Plymate, indicate that thyroxin depresses the division rate of chick fibroblasts *in vitro.* These observations, however, as yet unpublished, need confirmation. In a recent letter from which I quote with his permission, Dr. Carrel writes: "We never observed any acceleration in cell multiplication by using thyroxin in cultures of fibroblasts and other cells." Experiments during the past summer (1927) with the eggs of such widely divergent forms as the

sea urchin *Echinometra* and the ascidian *Phallusia* establish a similar conclusion on a broader foundation of evidence and suggest the probability that depression of division rate may be a characteristic effect of thyroxin on animal cells in general. This evidence will be given below in detail, along with evidence of depression of differentiation rate as well. In neither case does the effect appear to be referable directly to the iodine content of the thyroxin molecule.

Echinometra lucunter and *Phallusia nigra* are abundant at the Tortugas. Both were breeding in August. Eggs and sperm were discharged by *Echinometra* promptly in the laboratory. They were removed from the gonoducts of *Phallusia*. In both cases, fertilization was initiated within ten minutes of the laying or taking of the eggs. The latter were transferred in approximately equal numbers to finger bowls each containing 100 cc. of sea water to which thyroxin had been added in concentrations from 1 part in 50,000 to 1 part in 1,600,000. In both experimental and control bowls the initial pH of the water was approximately 8.4. The temperature varied about 5 degrees during the twenty-four hours and often reached 29-32 degrees C. during the warmest part of the day. These high temperatures tended to shorten the interval between successive cleavages and thus probably to obscure somewhat the thyroxin effect.

The solution of thyroxin was prepared by placing in a watch glass a few milligrams of the crystalline product furnished by E. R. Squibb and Sons, adding 2 to 4 drops of N/10 NaOH—in which it dissolved—transferring this by pipette to a few centimeters of rain water containing a drop or two of N/10 NaOH and mixing this with the amount of sea water necessary to make the dilution required. In the first few experiments the controls were made up with rain water and NaOH to duplicate in these respects the thyroxin solutions. Later, these precautions were found to be unnecessary and were discontinued.

To obtain an accurate estimate of the effect of thyroxin on the division rate, continuous observations on given eggs in both experimental and control dishes possess obvious advantages. For several reasons, this method was not feasible in these experiments. Besides mechanical difficulties easily avoidable in another season, the failure of the eggs in one lot to cleave simultaneously was a source of embarrassment. The eggs often showed wide variations of cleavage from unsegmented eggs to the 64 cell stage in both thyroxin and control dishes.

Under the circumstances, the following method was used, which, though not ideal, was sufficiently precise to establish the essential facts. Samples of eggs were withdrawn with pipettes from one dish after another and examined in watch glasses or on slides. Experimental and control eggs were compared with reference to: the time at which the first cleavage occurred; the ratio of segmented to unsegmented eggs; the most advanced stage at a given time; the beginning of gastrulation; the activities and differentiation of the larvae. The last item obviously refers to the progress of differentiation and development rather than to the cleavage rates of the blastomeres. In some cases, hasty inspection was sufficient to establish the relative rates at which cleavage and development were taking place. In most cases, all the eggs in each sample drop were counted and classified with reference to the stage of cleavage they had reached. It was

thus clear for a given sample how many cells of the total number were unsegmented, how many were in the 2-cell stage, the 4-cell stage, and so on.

EXPERIMENTS WITH ECHINOMETRA LUCUNTER

The *effect of thyroxin in a concentration of 1:50,000* is typically displayed in one of the early experiments. The eggs laid by a single female at 11:35 A. M. were fertilized immediately. Ten minutes later they were transferred to dishes containing thyroxin in a concentration of 1:50,000, and to control dishes. The progress of the experiment is recorded in the accompanying table which includes: several counts of both thyroxin (T) and control (C) eggs, with the number in each cleavage stage, and the per cent. in process of segmentation.

TABLE 1

Time		No. Eggs	No.	No.	No.	%
Aug. 4	Lot	counted	2-cell	4-cell	8-cell	Segm.
12:40—1:03 p.m.	T	363	21	7	0	7.7
	C	406	28	14	0	10.3
1:07—1:27 p.m.	T	229	31	23	1	24.0
	C	251	33	25	2	23.9
1:30—1:54 p.m.	T	164	14	17	0	20.0
	C	256	19	60	10	34.7
Totals	T	756	66	47	1	15.0
	C	913	80	99	12	20.9

At 8:00 A. M., August 5, 25-40 per cent of the controls were swimming up. These swimming forms included spherical, ovate and angular larvae, the latter with skeletal spicules. In the thyroxin cultures, fewer than 1 per cent were moving. Some were swimming up. These included spherical and ovate forms. There were no angular forms. Most of the eggs were on the bottom disintegrating.

The eggs of another female were laid at 3:30 P. M. and fertilized five minutes later. At 5:30 P. M., repeated sampling showed that less than 20 per cent of the thyroxin eggs had segmented while all of the controls had done so. By 6:30 P. M., many of the latter had become blastulae; but there was no comparable development of the thyroxin eggs which were already showing certain cortical abnormalities and had begun to disintegrate by the following morning.

These results are typical. It appears, therefore, that *thyroxin in a concentration of 1:50,000 completely inhibits the cleavage of the majority of the eggs of Echinometra and hastens their disintegration, that it retards the cleavage and embryonic development of others which go on to gastrulation, and that it does not accelerate the cleavage of any of them.*

Thyroxin in a concentration of 1:75,000 produces similar though somewhat less marked results. More eggs segment, and disintegration is farther deferred. Those eggs that do segment, however, do so more deliberately than the controls and develop as far as gastrulation more slowly. In one lot of eggs, on the

morning following fertilization, many were found on the bottom unable wholly to free themselves from their membranes. Constricted into irregular dumbbell forms for the most part, they continued to differentiate for a time, developing skeletal spicules but failing to become normal larvae.

This abnormality occurred only twice in my experiments, in both cases in solutions of thyroxin made up from the same vial of crystals. It was noted at the time that this lot of thyroxin dissolved less readily than was customary, which further suggested a departure from standard that was probably responsible for the abnormal eggs.

In thyroxin at a concentration of 1:100,000, six lots of eggs from six different females gave similar results. The essential facts as observed in three of them are recorded in Tables 2, 3 and 4. The other lots add nothing of pertinent interest.

TABLE 2

EGGS LAID AND FERTILIZED AT 10:45 A. M.

Time	Thyroxin			
	1:100,000	1:200,000	1:400,000	Control
11:43 a. m.				Among 80 4 2c
11:48	No 2c	2c seen		
11:53			Among 475 30 segm	Among 144 32 segm
12:05 p. m.		Among 142 32 2c 1 4c		Among 64 24 2c 4 4c
12:10	Among 255 7 2c 2 4c			
12:15		Among 100 38 2c 4 4c		Among 120 103 2 and 4c
12:30			No 8c	Several 8c
12:35		2 8c		
12:40	Among 100 4 2c 0 4c			Among 123 20 2c 70 4c 4 8c
1:05	0 16c	0 16c	1 16c	Several 16c
2:15	Mostly unseg. few 4 and 8 c	Many 16c few 32c	Largely 16 and 32c	Spherical blastulae

TABLE 3
EGGS LAID AND FERTILIZED AT 11:00 A. M.

Time	Thyroxin			
	1:100,000(T_1)	1:200,000(T_2)	1:400,000(T_3)	Control (C)
11:55 a. m.	Among 75 11 2c			Among 60 50 2c
12:05 p. m.		Among 81 49 2c 2 4c	Like C	Among 85 74 2c 1 4c
12:09	Among 75 53 2c 2 4c			
12:20	Among 100 14 4c			Among 85 20 4c 1 8c
12:25		1 8c		
1:00	Many 2, 4, 8c few 16c			Among 100 66 8c 34 16c
1:30	Behind C	16c, 32c	16c, 32c	Like T_2, T_3
4:50	Not swimming large cells	Swimming, behind C	?	Swimming
8:30	Swimming, spherical	Like C	Like C	Actively swimming, elongated
9:00 a. m.	Gastrulae, not angular	Not angular	More advanced than T_2, less than C	Angular, compressed

TABLE 4
EGGS LAID 12:30 P. M.; FERTILIZED 12:40 P. M.

Time	Thyroxin			
	1:100,000(T_1)	1:150,000(T_2)	1:300,000(T_3)	Control
1:50 p. m.	2c, 4c present	2c, 4c present	2c, 4c present	2c, 4c present
2:30	Among 100 20 4c fewer 8c than in C			Among 100 50 4c more 8c than in T_1
2:40		Occasional 16c	Like C	More 8 and 16c than in T_2
3:20	2, 4, 8, 16c occasional 32c			Among 100 50 32c
3:40		Behind C	Behind C	
8:00	Not swimming	Not swimming	Swimming spherical ovate	Much larger prop. larvae swimming
8:00 a. m.	Spherical inactive	Like T_1	Ovate and helmet sh.	Flattened angular advanced over T_2

Thyroxin in a concentration of 1:133,000 produced comparable results, in two lots of eggs. In the first, eggs laid and fertilized at 10:00 A. M. were transferred to thyroxin at 10:40 A. M. By 1:00 P. M. several eggs had reached 16- and 32-cell stages in the control dishes, while none had passed beyond the 8-cell stage in thyroxin. On the following morning, the eggs in thyroxin were apparently in good condition, but distinctly behind the controls in development. In the second, eggs laid at 10:30 A. M. fertilized at 10:40 A. M. and transferred to thyroxin at 11:15 A. M. had not reached the 16-cell stage by 1:00 P. M., although the controls had. At 3:15 P. M., this lag was further apparent in the distinctly lower average cleavage of the former. On the following morning, both thyroxin and control eggs were swimming abundantly; but the former were spherical, the latter helmeted and angular.

Thyroxin in a concentration of 1:150,000 produced similar results in two other lots of eggs, notes regarding one of them being recorded in Table 4. The eggs of the other lot were laid and fertilized at 2:10 P. M. At 3:27 P. M., among 50 thyroxin eggs, 10 were in the 2-cell stage, 1 in the 4-cell stage; among 78 control eggs, 13 were in the 2-cell stage, 5 in the 4-cell stage, and 2 in the 8-cell stage. By 4:30 P. M., 16- and 32-cell stages had appeared among the thyroxin eggs, but were fewer in number and less regular and compact than in the controls. On the following morning, there were gastrulae among both thyroxin and control eggs, but the latter were more advanced.

Thyroxin in a concentration of 1:200,000 was given to five lots of eggs. Its retarding effect on cleavage in two of these is early apparent in Tables 2 and 3. In a third lot, abnormalities occurred to which reference has already been made as having been due probably to an impurity or variation in the thyroxin itself. In the other lots, there was no retardation of early cleavage, it being apparent only after 4 to 5 hours. Otherwise, the eggs of all lots reacted similarly.

Thyroxin in a concentration of 1:300,000 was given to three lots of eggs. Its retarding effect is still apparent, but less pronounced. One lot of eggs is recorded in Table 4. Another, laid and fertilized at 10:00 A. M. and transferred to thyroxin at 10:15 A. M. showed, at 12:45 P. M. in a sample of 20 eggs, 5 in the 2-cell stage and 4 in the 4-cell stage; while in a sample of 24 eggs from the control, 21 were in the 4- (or 8-) cell stage. Both thyroxin and control eggs were cleaving well at 2:50 P. M., many in the 64-cell stage being present in each group. At 10:15 A. M. of the following day, both were swimming up abundantly and apparently in excellent condition. The thyroxin eggs had now become rounded and also angular larval forms; but they were less advanced than the controls, there being more angular forms and a greater differentiation of these among the latter. Twenty-four hours later, the thyroxin eggs were still behind the controls. On the following morning, the former were dead, the latter in good condition. In the third lot of eggs, laid and fertilized at 1:45 P. M. (with sperm that had been discharged an hour before), there was little to choose between thyroxin eggs and controls at 3:30 p. m. Both were cleaving abundantly. There were traces of irregularity in the cleavage of the former, but no lag. By the next morning, however, though a cloud of healthy larvae was afloat in both thyroxin and control dishes, the former contained relatively very few angular forms, the latter many and characteristically flattened.

Of the four lots of eggs exposed to thyroxin in a concentration of 1:400,000, two appear in Tables 2 and 3. The other lots tell essentially the same story. In one of them there was a lag in cleavage among the thyroxin eggs similar to what may be noted in Table 2. In the other, no lag was recognized. On the following morning, in both lots, many eggs had become young plutei, with shorter arms in the thyroxin cultures than in the controls.

A single lot of eggs was treated with thyroxin in a concentration of 1:600,000. During the first day, no differences were noted between thyroxin and control eggs. On the following morning, the controls were again in the lead.

This completes our observations on the effect of thyroxin on sea urchin eggs. The data may be summarized by saying that while they provide no evidence for an accelerating effect of thyroxin on either the cleavage or the differentiation of these eggs, they do support the conclusion that in the concentrations used, thyroxin depresses the processes of both differentiation and division, to a degree varying with the concentration.

The mechanism of this effect is not clear. That the iodine of the thyroxin molecule is not the essential factor seems probable from the following observations on the effects of potassium iodide in much higher concentrations. In a concentration of 1:42,750 KI, which represents, in terms of iodine, a thyroxin solution of 1:50,000, *Echinometra* eggs kept step with the controls, cleaving as early and as rapidly and being as far advanced at the end of 24 hours, and living as long.

Eggs raised in 1:855 KI developed almost as satisfactorily, remaining practically abreast of the controls for 8 hours, swimming up vigorously as helmet forms at the end of 24 hours, and living for another 24 hours, developing in the meantime skeletal spicules—but no arms. The controls at that time were well developed plutei.

Eggs raised in 1:300 KI equalled the controls for 4 hours after fertilization. Three hours later, they resembled the controls in form but were less active.

EXPERIMENTS WITH THE EGGS OF PHALLUSIA NIGRA

In Table 5 are summarized the observations on a mixed lot of eggs taken from the oviducts of six individuals, fertilized by sperm

from two others at 11:27 A. M., and distributed at 11:35 A. M. to 4 dishes containing thyroxin in concentrations running from 1:50,000 to 1:200,000 (T_1-T_4), and one control dish (C). The figures in each column refer to the number and cleavage stage of all eggs found by inspection of sample drops to be in cleavage at the time specified. In three cases only, total counts are indicated. Such figures do not provide an adequate picture of relative proportions, but they are not without value in this connection. It should be remembered, further, that the time at which a cleavage stage was first observed is not necessarily the time at which the cleavage occurred.

The outstanding facts in this table are:

1. The small number of eggs segmenting in thyroxin. Not more than 5 per cent had segmented in any of the dishes 2.5 hours after fertilization, as against 85 per cent in the controls.

2. The lag in the cleavage of the eggs in 1:500,000 thyroxin.

TABLE 5

Time	Thyroxin				
	T_1 1:500,000	T_2 1:100,000	T_3 1:150,000	T_4 1:200,000	Control
11:44 a. m.	0				
12:15 p. m.		In 50, 2 8c			
12:20				1 4c, 1 8c	Sev. 2 and 4c 2 8c
12:27–30	1 4c	1 8–16c	1 2c, 1 4c 1 16c		2 2c, 1 4c 1 8c, 1 16c
12:35				1 16c	
12:40	1 8–16c				
12:45–50		1 2c, 2 4c, 1 8c	1 4c, 2 16c, 1 32c		Numerous 2c sev. 4c, 8c, 16c, 3 32c
1:00–08			In 100, 1 8c, 2 32c		In 100, 9 2c, 7 4c, 5 8c, 1 16c, 1 32c
1:20	No more seg.	No more seg.	No more seg.	No more seg.	
1:55	No more seg.	No more seg.	No more seg.	No more seg.	In 100, 88 seg.

The events of the first two hours of another experiment are summarized in Table 6. The eggs were taken from 10 animals, mixed and fertilized by sperm from 4 others at 11:27 A. M. and then transferred to experimental and control dishes. The former contained thyroxin in concentrations of 1:200,000 (T_1), 1:300,000 (T_2), 1:400,000 (T_3), 1:500,000 (T_4), 1:600,000 (T_5), 1:800,000 (T_6), 1:1,000,000 (T_7), 1:1,200,000 (T_8), 1:1,600,000 (T_9), 1:2,000,000 (T_{10}).

TABLE 6

Time	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}	Control
12:15 p. m.	0	0									
12:20–24			Sev. 2c	Sev. 2c	0	Sev. 2c					
12:27–30	0	Sev. 2c	Sev. 2c	Sev. 2c	0	Sev. 2c			Sev. 2c 1 4c		Num. 2 and 4c
12:33–36		Sev. 2c 2 4c	Sev. 2c 3 4c				2 4 c				More in cleavage
12:38–43	1 2c							Sev. 8c			Sev. 8c
12:44–48					Sev. 2c Sev. 4c		Sev. 4c 1 8c	2 4c	2 4c 2 8c		
12:50–52	2 4c	Sev. 4c 1 16c		Sev. 2, 4, 8c 1 16c							Num. 2, 4, 8c Sev. 16c
12:58–1:03	Sev. 4c Sev. 8c 1 16c										Sev. 32c
1:05–10		2, 4, 8c 1 16c	2, 4, 8c Sev. 16c	2 to 16c 1 32c	2 to 32c	2 to 32c	2 to 32c		64c?		Sev. 32c More Cl.
1:16	1 32c										64c

The farther history of this experiment follows:

T_1 (1:200,000)

1:30 p.m. 11 of 104 eggs cleaving: 2 2c, 1 4c, 3 8c, 2 16c, 3 32c.
2:35 12 of 79 eggs cleaving.
3:40 As at last reading.
4:50 A few larvae; many undivided eggs, as before.
6:45 Larvae farther advanced; otherwise as before.

T_2 (1:300,000)

1:36 p.m. 19 of 95 eggs cleaving: 7 2c, 5 4c, 3 16c, 3 32c, 1 64c.
2:35 27 of 37 eggs cleaving.
3:40 50 of 58 eggs cleaving.
4:50 Farther advanced than T_1; many more larvae.

T_3 (1:400,000)

1:41 p.m. 29 of 66 eggs cleaving: 4 2c, 12 4c, 2 8c, 5 16c, 4 32c, 2 64c.
2:35 50 of 59 eggs cleaving.
3:40 50 of 55 eggs cleaving.
4:50 Larvae more advanced than in T_2.

T_4 (1:500,000)

1:47 p.m. 44 of 78 eggs cleaving: 6 2c, 6 4c, 5 8c, 11 16c, 15 32c, 1 64c.
2:45 99 of 104 eggs cleaving.
3:40 56 of 60 eggs cleaving.
4:50 Larvae with longer tails than in T_1-T_3; as in C.

T_5 (1:600,000)

1:53 p.m. 34 of 72 eggs cleaving: 10 2c, 6 4c, 4 8c, 7 16c, 7 32c.
2:45 95 of 100 eggs cleaving.

T_6 (1:800,000)

2:00 p.m. 42 of 63 eggs cleaving: 4 2c, 7 4c, 7 8c, 10 16c, 12 32c, 2 64c.
2:45 50 of 55 eggs cleaving.
3:40 Not distinguishable from C.

T_7 (1:1,000,000)

2:30 p.m. 95 of 100 eggs cleaving: all stages.
4:50 As in C.

T_8 (1:1,200,000)

2:30 p.m. 100 of 100 eggs cleaving: all stages.
4:50 As in C.

T_9 (1:1,600,000)

2:19 p.m. 49 of 68 eggs cleaving: 8 2c, 2 4c, 4 8c, 6 16c, 7 32c, 12 64c. 10 gastrulae.
2:55 97 of 100 eggs cleaving.
4:50 As in C.

T_{10} (1:2,000,000)

2:15 p.m. 15 of 27 eggs cleaving: 3 2c, 2 4c, 2 8c, 1 16c, 2 32c, 1 64c, 4 gastrulae.
2:53 100 of 100 eggs cleaving.
4:50 As in C.

C

2:06 p.m. 53 of 82 eggs cleaving: 14 2c, 8 4c, 3 8c, 3 16c, 4 32c, 1 64c, 20 gastrulae.
2:51 59 of 61 eggs cleaving.
3:40 100 of 100 eggs cleaving.
4:50 Larvae as in T_1-T_{10}.
6:45 A very few larvae have emerged.

It appears from these records that thyroxin in a concentration of 1:200,000 (T_1), produced the following effects that set it rather apart from the rest: cleavage began later and involved fewer eggs, gastrulation occurred later, and the larvae present 5.5 hours after fertilization were inferior both in number and in development. The control (C) was distinguished by the largest proportion of cells involved in cleavage from the beginning; and was surpassed in no respect by any of the others. The latter, though very much alike, are divisible into two groups, the dividing line running between T_3 and T_4. The first group, including T_2 and T_3, was a bit retarded both as to rate of cleavage and the rapidity with which the maximum number of eggs to cleave was attained. As for the second, including T_4-T_{10}, there was little to distinguish one lot of eggs from another except with reference to the last point. In a concentration, then, of 1:500,000 or more, thyroxin had little or no effect on the course of cleavage or development.

One more experiment will be considered. Eggs from eight animals were mixed and fertilized by sperm from four, at 11:00 A. M. In ten minutes, they were distributed to dishes containing concentrations of thyroxin varying from 1:200,000 to 1:1,000,000, and one control dish containing sea water only. The course of events in each dish as determined by means of sample drops will be given first, to be followed by tabulations and comment.

T_1 (1:200,000)

11:40 a.m.	Among 50 eggs, 1 4-cell stage.
12:05 p.m.	Among 47 eggs, 1 16-cell.
1:05	An occasional gastrula; no cleavage stages.
1:30	An occasional 64-cell stage or gastrula; many dead eggs.
3:00	Among 100 eggs, 10 have cleaved.
6:40	These are now larvae, still within egg membranes.

T_2 (1:250,000)

11:40 a.m.	Among 50 eggs, 2 2-cell, 1 4-cell stage.
12:06 p.m.	Among 33 eggs no cleavage stages.
1:07	As in T_1.
1:22	Among 52 eggs, 6 gastrulae.
3:00	Among 100 eggs, 15 have cleaved.
6:40	As in T_1.

T_3 (1:300,000)

11:48 a.m.	Among 79 eggs, 1 2-cell, 2 4-cell stages.
12:07 p.m.	Among 35 eggs, 1 8-cell, 2 16-cell.
1:09	As in T_1, with perhaps more gastrulae.
1:34	Among 53 eggs, 11 gastrulae.
3:00	Among 100 eggs, 12 have divided.
6:40	As in T_1.

T_4 (1:350,000)

11:44 a.m.	Among 100 eggs, 2 2-cell, 4 4-cell.
12:08 p.m.	Among 50 eggs, 1 2-cell, 1 4-cell, 1 8-cell, 3 16-cell.
1:11	16-, 32-, 64-cell and gastrulae present.
1:36	Among 34 eggs, 6 gastrulae.
3:00	Among 61 eggs, 13 have divided.
6:40	As in T_1.

T_5 (1:400,000)

11:50 a. m.	Among 48 eggs, 2 4-cell, 1 8-cell.
12:10 p.m.	Among 47 eggs, 2 2-cell, 1 4-cell, 1 8-cell.
1:14	Among 35, 11 have cleaved: 2 to 64-cell stages.
1:37	15 of 51 eggs have cleaved; mostly gastrulae.
3:00	20 of 47 have cleaved.
6:40	Larvae, in advance of T_4

T_6 (1:450,000)

11:45 a.m.	Among 100 eggs, 3 2-cell, 1 4-cell.
12:12 p.m.	Among 59 eggs, 1 4-cell, 1 8-cell, 1 16-cell, 2 32-cell.
1:16	Among 70 eggs, 1 16-cell, 10 gastrulae.
1:40	12 of 39 have cleaved.
3:00	Larvae in egg membranes.
6:40	Larvae slightly in advance of T_5.

T_7 (1:500,000)

12:04 p.m.	Among 77 eggs, 1 2-cell, 1 4-cell, 1 8-cell, 1 16-cell.
12:21	Among 49 eggs, 4 2-cell, 3 4-cell.
1:19	Among 33 eggs, 13 have cleaved; mostly gastrulae.
1:42	22 of 33 eggs have cleaved; all stages.
3:00	50 of 100 eggs have cleaved.
6:40	Larvae slightly in advance of T_6.

T_8 (1:600,000)

11:53 a.m.	Among 54 eggs, 2 4-cell, 3 8-cell.
12:19 p.m.	Among 66 eggs, 2 2-cell, 2 4-cell, 1 16-cell, 2 32-cell.
1:21	20 of 45 eggs have cleaved; various stages, including several gastrulae.
1:44	19 of 55 eggs have cleaved.
3:00	20 of 41 eggs have cleaved.
6:40	Larvae slightly in advance of T_7.

T_9 (1:800,000)

11:56 a.m.	Among 64 eggs, 2 8-cell.
12:23 p.m.	Among 13 eggs, 1 32-cell.
1:23	18 of 31 eggs have cleaved; 9 gastrulae.
1:46	26 of 38 eggs have cleaved; all stages.
3:00	90 of 100 eggs have cleaved.
6:40	Larvae slightly in advance of T_8.

T_{10} (1:1,000,000)

11:58 a.m.	Among 32 eggs, 6 2-cell, 2 4-cell, 1 8-cell.
1:25 p.m.	41 of 56 eggs have cleaved; all stages, many gastrulae.
1:48	26 of 34 eggs have cleaved; all stages.
3:00	75 of 85 eggs have cleaved.
6:40	Larvae a little ahead of T_9-T_8.

C

11:44 a.m.	Among 100 eggs, several 2-cell, several 4-cell.
12:01 p.m.	Among 65 eggs, 10 2-cell, 2 4-cell, 2 8-cell, 3 16-cell.
12:14	Among 53 eggs, 10 2-cell, 9 4-cell, 3 8-cell, 2 16-cell, 3 32-cell.
1:27	38 of 43 eggs have cleaved; all stages, including many gastrulae.
1:50	91 of 100 eggs have cleaved.
3:00	100 of 100 eggs have cleaved.
6:40	Larvae as in T_{10}.

These lots of eggs fall into two groups, defined by the amount of thyroxin in solution, by the number of eggs in process of cleavage at 3:00 P. M., and by the rate at which that maximum was attained.

In Group 1 are T_1-T_4, with thyroxin from 5.00 to 2.85 mgm. per L.
In Group 2 are T_5-T_8, with thyroxin from 2.50 to 1.66 mgm. per L.
In Group 3 are T_9-T_{10}, with thyroxin from 1.25 to 1.00 mgm. per L.
In Group 4 is C.

Cleavage was observed as early in Groups 1-3 as in Group 4, not, however, in as many eggs. Succeeding stages appeared, also, about as early in Groups 1-3 as in Group 4, again, however, in smaller numbers. In Group 1, only 10-21 per cent of the eggs had cleaved by 3:00 P. M.; in Group 2, about 43 per cent had done so; in Group 3, 89 per cent; in Group 4, 100 per cent.

Table 7 indicates the progress of cleavage in all lots of eggs up to 3:00 P. M. The numerator of each fraction represents the number of eggs in cleavage in a given sample, the denominator the total number of eggs counted.

By 6:40 P. M., there were tailed embryos in all dishes. Those in T_1-T_4 were in about the same stage of development, still within the egg membrane. Those in T_5-T_{10} were more advanced, progressing very gradually from T_5 to T_{10}. C was clearly in the lead in that about 10 per cent of the larvae had emerged.

The foregoing data are the basis for the following conclusions:

1. Thyroxin affects the eggs of *Echinometra* and *Phallusia* similarly.

2. It accelerates neither cleavage rate nor the processes of differentiation.

TABLE 7

Time	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	T_{10}	Control
11:40–49	1/50	3/50	3/79	6/100		3/100					More 2 and 4c
11:50–59					3/48			5/54	2/64	9/32	
12:00–09	1/47		3/35	6/50							
12:10–19					4/47	5/59		7/66			26/53
12:20–29							7/49		1/13		
1:00–09	Few	See T_1	See T_1								
1:10–19				More than T_3	11/35	11/70	13/33				
1:20–29								20/45	18/31	41/56	38/43
1:30–39		6/52	11/53	6/34	15/51						
1:40–49						12/39	22/44		26/38	26/34	91/100
3:00	10/100	15/100	12/100	13/61	20/47		50/100	20/41	90/100	75/85	100/100

3. On the contrary, it *retards* both cleavage rate and differentiation.

4. This effect varies in degree with the concentration of thyroxin.

5. It is not due primarily to the iodine in the thyroxin molecule.

6. Since thyroxin depresses cell division in such widely different organisms as *Paramecium, Echinometra* and *Phallusia,* it may well be that it is a depressant of cell division throughout the animal kingdom.

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EFFECTS OF ULTRAVIOLET LIGHT ON PARATHYROIDECTOMIZED RATS

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The purpose of this paper is to report briefly some experiments on the effect of ultraviolet light upon thyroparathyroidectomized albino rats. Similar experiments have already been done by Swingle and Rhingold (1) upon the dog. The rat is in some ways a more convenient subject, and the general interest at the present time in the therapeutic application of ultraviolet light, as well as the possibility that such work might help to elucidate the physiology of the parathyroids, seemed to justify experiments on another variety of animal. However, the results here reported for the rat will be found to agree in general with those obtained for the dog.

In the preliminary experiments, the lack of sensitiveness of the rat to ultraviolet light became apparent. Through the cooperation of Miss Irene Smith of the Physiotherapy Department the author was enabled to use a number of mercury-vapor quartz lamps which are routinely used in the treatment of Dispensary patients. For these lamps, at a skin distance of 40 inches, an initial exposure of 3 minutes suffices to produce a marked erythema in the unhabituated human subject. An albino rat, however, whose back has been shaved, shows no obvious cutaneous or systemic reaction after an initial exposure of three hours at this distance. In these experiments it also appeared that thyroparathyroidectomized rats showed definitely deleterious effects after irradiations of from 3 to 30 minutes. In three instances, rats which had been in a condition of latent tetany had violent convulsions, terminating fatally, within an hour after the irradiation, and in other instances less severe attacks occurred within an hour after irradiation. It was possible that this might be due to the excitement of being transferred to fresh cages, carried downstairs to a strange room, and

stimulated by the odor of ozone and the bright visible radiations from the lamps.

In the final experiments, therefore, both controls and test animals were set under the lamps, the controls being shielded from the ultraviolet light by means of glass plates. In the first experiment 26 thyroparathyroidectomized rats were divided into two groups in such a way that the weights of the controls showed the same distribution as those of the test rats; the average weight for each of the two groups was 124 grams. Irradiations were begun on the day of the operation, and the observations, discontinued on the ninth day, showed positive results. The controls, which had been shielded from the ultraviolet wave lengths, had suffered more severely from tetany, had a higher mortality, and had lost six times as much in average body weight. A second experiment was then done with 13 rats. The irradiations were begun three days before operation. The results were again positive. When the observations were discontinued 48 hours after operation, the mortality was nil for both groups, but the tetany had been less severe in the rats receiving ultraviolet light and they had lost only 2/3 as much in body weight as had the controls.

The conclusion is that ultraviolet light in daily doses about 50 times that used in the unhabituated human subject is beneficial to thyroparathyroidectomized white rats. It is difficult to say how much significance may be attached to this benefit. On the one hand, it is possible that the irradiation might have some favorable effect upon the body without a specific relationship to those phases of metabolism with which the parathyroids are specifically concerned. On the other hand, supposing a specific relationship to exist between the parathyroids and the irradiated skin, one could hardly expect very striking results from a slowly-acting therapeutic agent like ultraviolet light in a condition which progresses as rapidly as does the parathyroprival syndrome in the rat, so that the effects reported here and by others would seem to be significant. The experiments of Reed and Tweedy (2), who found no alterations in the blood calcium level when the blood was directly irradiated in anesthetized dogs; of Mayerson, Gunther, and Laurens (3), who did not find any rise in blood calcium during the first 8 days of

irradiation; of Swingle and Rhingold (1), who found that the positive results of their irradiation experiments were not accounted for by any appropriate changes in the blood calcium; and of Denis and Corley (4), who found no increase of calcium in either tissues or blood after irradiation with or without simultaneous administration of excess calcium—all seem opposed to the supposition that calcium is primarily concerned in this effect. It is generally agreed that the disturbance of calcium metabolism in rickets is not primary. Similarly there are many objections, which have been summarized by Dragstedt (5), to the assumption that a disturbance of calcium metabolism is the only fundamental factor in the genesis of parathyroprival tetany. These considerations suggest that the parathyroids have some function which is only secondarily related to calcium metabolism and which is in some way related to the photochemical function of the skin.

SUMMARY

Ultraviolet light in sufficiently large doses is beneficial to thyroparathyroidectomized white rats. Unless the experiment is carefully controlled, this favorable effect is overshadowed by the unfavorable effect of handling and bright lights upon rats in latent tetany.

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ON THE STORAGE OF SULPHUR IN THE ADRENAL GLANDS

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Recent work, both abroad and in our own laboratory, has pointed to some relationship between the adrenal glands and sulphur metabolism. Data gathered from the literature seemed to indicate that the content of sulphur found in the adrenals is higher than in the other organs. To quote briefly some of these references, we mention Schultz (1) who found 0.964 per cent sulphur in the liver, 0.7797 per cent in the spleen, and 0.8608 per cent in the muscle tissue. Other figures (2) show that the sulphur content in the liver varies from 0.75 to 1.1028 per cent in man, while in the ox it might be as high as 1.86 per cent. In the liver from 0.9643 to 2.5 per cent in man, and 1.75 per cent in the ox. In the spleen (3) the figures seem to vary from 0.7797 per cent in man to from 1.72 to 2.23 per cent in the ox.

Work done by Katz (4) seems to give more uniform figures for the various species inasmuch as the percentage of sulphur content of muscle tissue is as follows: In man, 0.75; pig, 0.85; ox, 0.77; rabbit, 0.85; dog, 0.96; cat, 0.87; hen, 0.92; pike, 1.05.

As to the adrenal, we can refer to Aufrecht and Diesing (5) who found 3.67 per cent sulphur in the adrenals, without mentioning whether they examined human adrenals or those from an animal. Other authors do not agree with this high figure (6) (Loeper 1-1.1), but the consensus of opinion seems to be that there is considerably more sulphur in the adrenal gland of the same animal than in its other organs (7). Furthermore, it seems that this excess of sulphur is stored up particularly in the cortex of the adrenal gland. Loeper (8), who has recently made extensive investigations of the function of the adrenal in sulphur metabolism, also claims that the blood of the suprarenal vein contains from one-eighth to one-third less sulphur than the arterial blood. As the amount of sulphur in the blood after removal of the adrenals increased from 0.22 to 0.894 per cent,

Loeper (9) claimed that the adrenal fixed the sulphur in its tissue and probably also in distant tissues.

Recent work done in our laboratory by Foldes (10) on the influence of sulphur on carbohydrate metabolism has shown that repeated sulphur inunction increased the size of the adrenal gland in the rabbit, while simultaneously its sulphur content also increased. In order to establish whether in case of sulphur administration the sulphur content of various organs increases or whether we are dealing with a specific function of the adrenal gland, the following experiments have been carried out.

White rats were given daily inunctions of sulphur ointment for a period of a month. The ointment was rubbed into the skin for 15 to 20 minutes on an area comprising about one-third of the back. In these animals the sulphur content of liver, spleen, kidney, muscle tissue and adrenal glands was examined, and the results were compared with those obtained in a number of healthy rats of our stock which did not receive any treatment whatever.

The procedure to determine the sulphur content was as follows: The organs were dehydrated in absolute alcohol, then minced and dried in the desiccator over calcium chloride for 12 hours, with the help of a vacuum pump. The dried substances were weighed and each dissolved separately in hot nitric acid. To this solution, according to the weight of the substance, from 5 to 10 cc. of Benedict's solution was added. The mixture was evaporated in a porcelain dish on an electric stove. The dishes, with the remaining dry and black residue, were heated over a Bunsen burner from 10 to 15 minutes. After cooling, a 4 per cent hydrochloric acid solution was added and heated until a completely clear solution was obtained. Ten cc. of a 10 per cent solution of barium chloride were added and left to stand for a few hours, then filtered through a very fine meshed, retentive filter paper. This filter paper was put into a small porcelain crucible, dried in an oven, and heated over a Bunsen burner until complete combustion. The Benedict's solution was examined for any possible sulphur content, but hardly any traces were found.

In five normal rats the following percentages of sulphur were found:

Liver: 0.82, 0.71, 0.71, 0.68, 0.76. The average being 0.736.

Spleen: 0.712, 1.06, 0.77, 0.89, 0.85. The average being 0.856.

Kidney: 0.868, 0.820, 0.832, 0.801, 0.842. The average being 0.832.

Muscle: 0.682, 0.72, 0.73, 0.728, 0.74. The average being 0.72.

The determination of the sulphur content of the adrenal glands was made on 28 normal animals. Taking into consideration the small size of the adrenal gland in the rat we used in our first determination 10 pairs of adrenal glands and obtained a percentage of 1.6 of sulphur. With another set of 10 animals, we got the percentage of 1.55. The next experiment was done on the glands of 4 animals yielding a percentage of 1.48. With two pairs, a percentage of 1.51 was obtained, and 2 determinations, each done on a single pair of adrenal glands, yielded the figures of 1.49 and 1.47.

According to these findings the average sulphur content of the adrenal glands in the rat can be put at 1.52. While these data do not agree with the figure given by Aufrecht and Diesing, they are nearer to those mentioned by Loeper, although somewhat in excess of the latter.

In the sulphur treated animals the following percentages of sulphur were found in the different organs:

Liver: 0.916, 0.85, 0.823, 0.75, 1.01, 0.913, 0.82, 0.843, 0.914, 0.892. These figures vary from 1.01 to 0.75, with the average 0.893.

Spleen: 1.06, 1.4, 1.327, 1.1, 1.09, 0.996, 1.19, 1.02, 1.12, 1.101. These figures vary from 1.4 to 0.996, the average being 1.14.

Kidney: 1.04, 0.85, 0.874, 0.76, 1.18, 1.03, 0.932, 0.912, 0.946, 0.887. These figures vary from 1.18 to 0.85, the average being 0.941.

Muscle: 1.101, 0.98, 0.962, 0.7, 1.14, 0.842, 0.78, 0.823, 0.865,

0.812. These figures vary from 1.14 to 0.78, the average being 0.8914.

The adrenals were examined in the following order: Those of the first 2 animals were each examined separately. The figures obtained were 3.35 and 3.8 per cent respectively. The next 6 animals were examined in two groups each of 3. The percentage found was 3.90 and 3.16. The remaining two pairs of adrenals examined together gave a percentage of 3.42. Thus the figures obtained for the adrenal vary from 3.16 to 3.90, with an average of 3.526.

In comparing the figures obtained in our experiments it appears that the amount of sulphur in the liver, spleen, kidneys and the muscle tissue does not increase at all, or at least not considerably. On the other hand, the increase of sulphur in the adrenals is a striking one, ranging from 100 to 150 per cent. It seems, therefore, that the adrenal gland is the only organ examined so far capable of storing sulphur which has been introduced into the body. The sulphur in question is obviously not a part of the protein molecule. However, we are not able to tell in what form such sulphur is deposited. These findings, together with those of Loeper, seem to establish a hitherto unknown function of the adrenal gland, which is probably connected to its cortical portion. This "thiopexique" function of the adrenal cortex may have some bearing on carbohydrate metabolism, according to the experiments carried out in our laboratory by Foldes (11).

SUMMARY

The sulphur content of various organs of the normal rat, and of rats which had received repeated inunctions of sulphur, was examined.

Small amounts of sulphur were retained in the organs of the latter animals.

The physiological sulphur content of the adrenal gland is higher than that of the other organs, and after sulphur administration its increase is considerable.

In conclusion, I wish to express my sincere thanks to the

head of the laboratory, Professor M. Goldzieher, for his kind advice and assistance.

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Abstract Department

Addison's disease and diabetes mellitus occurring simultaneously. Arnett, J. H., Arch. Int. Med. **39**: 698-704. 1927.

A rare and possibly unique case is reported, believed to represent the simultaneous existence of two mutually antagonistic conditions, Addison's disease and diabetes mellitus. The diagnosis of diabetes was based upon the presence of hyperglycemia, glycosuria, ketonuria, and at times a diminished plasma CO_2 with symptoms of impending coma. The diagnosis of Addison's disease was based upon excessive pigmentation of the skin (a microphotograph of which is shown), arterial hypotension, asthenia, vomiting, absence of one suprarenal gland and widespread changes in the other. Homochromatosis with diabetes (bronzed diabetes) was ruled out by the absence of iron-reacting pigment and the absence of extensive fibrosis of the abdominal organs, so characteristic of this disease. The outstanding therapeutic difficulties presented by this case were hypersensitivity to insulin (presumably due to the Addison's disease) and a tendency toward the rapid development of ketosis (probably dependent upon the presence of diabetes mellitus). Judged by this case, destructive radiation of the suprarenal glands, as is practiced in some of the German clinics as a treatment for diabetes mellitus, is not a justifiable procedure.—Author's Abst.

Blood sugar, adrenaline and sympathetic nervous system. A test for the excitability of the sympathetic. Delbaere, L. J., Nederl. Maandschr. v. Geneesk. **14**: 379-420. 1927. Abst., Chem. Absts. **21**: 3681.

The hyperglucemic effect of adrenaline is used as a test for the excitability of the sympathetic. After a theoretical discussion the results of tests are given: the hypodermic or intramuscular injection of 0.001 cc./kgm. 0.1% adrenaline immediately after a meal rich in carbohydrates increased the blood sugar of normal children by at least 0.1% within one-half hour after the injection. The response was less pronounced in convalescents from severe infections, especially those with high fever, and in children suffering from acute nutritional disturbances (decompensation Herter's infantilism), exudative diathesis, or acute rickets with or without tetany. Although it seems established that the vagus has no part

in the production of hyperglucemia, a few experiments in this direction were made. The slightly antagonistic effect of histamine is attributed to an inhibition of the sympathetic rather than to a stimulation of the vagus. Atropine had a slightly synergistic effect.

Researches on the sympathetic suprarenal lesions in some symptomatic depressive syndromes. De Leo, S., Neurologica **5**: 284. 1926. Abst., Arch. Neurol. & Psychiat. **18**: 622-628.

The author describes two cases of depression, one of which occurred in the course of a senile psychosis and the other in the course of general paralysis. In both cases he examined the sympathetic celia ganglia and the suprarenals. In the ganglion cells in the first case he found lesions of acute type leading to disintegration of the cell body. Lesions of the dendrites and of the axons were also found. In the suprarenals the most striking feature was degeneration of the medullary cells, a small infarct, and vacuolization of the cortical elements. In the second case, the lesions of many cells in the sympathetic ganglia were more of the atrophic type, while some cells showed fatty degeneration. Lesions of the dendrites and of the axons were also marked. In the suprarenal there was hyperemia of the zonia reticulata, besides a few small focal hemorrhages. The chromaffin cells were swollen, with homogeneous cytoplasm and degenerated and poorly stained nuclei. The lesions may, according to the author, have influenced the onset of the depressive features in the two types of psychoses. The lesion of the sympathetic ganglia particularly may influence the development of hypochondriac delusions, especially in patients with defective judgment, while the lesions of the suprarenals may facilitate the accumulation of toxic substances which act on the cerebral cortex. The depressive conditions at times accompanying Addison's disease suggest a suprarenal origin for the depressive syndrome.

Hyperadreninemia in fever (Ueber Hyperadrenalinämie bei Fieberzuständen). von Euler, U., Arch. f. d. ges. Physiol. **217**: 699-716. 1927.

Evidence is adduced that tissue oxidation is increased by increased adrenin action in fever.—A. T. C.

Action of the adrenal cortex on growth (Azione della corteccia surrenale sull' accrescimento). Fieschi, A., Tipografia Cooperativa 1-15: 1927.

Experiments on rabbits showed that feeding with adrenal cortex caused a greater development of the muscles and bones in experimental than in the control animals. The relative growth of

the trunk skeleton was greater than that of the limbs. The author believes this to be a hormone action of the adrenal cortex.—G. V.

Studies on vigor. IX. Ergographic studies on adrenalectomized animals. Gans, H. M. and H. H. Miley, Am. J. Physiol. **82**: 1-6. 1927.

A comparative ergographic study of the fatigability of the gastrocnemius muscles of 22 adrenalectomized and 18 normal rats was made. The absolute strength per gram muscle of the experimentals was slightly higher than that of the controls. The total work performed by the adrenalectomized animals before complete fatigue was only 1/16 of that of their controls.—Authors' Abst.

The diagnosis of adrenal tumors with classification of adrenal tumor syndromes, and report of cases. Gibson, T. E., J. Urol. **18**: 33-59. 1927.

This is a review with bibliography and a discussion of nine cases of adrenal tumor, four of which were primary. There are three types of clinical pictures from such tumors. (1) The genito-suprarenal type shows changes toward the adult male type of body, particularly of the genitalia. This is associated with a cortical tumor, either carcinomatous or benign. These may occur at any age. The medullary tumors, or neurocytoma, produce the other two types. (2) The Hutchison's type shows a metastasis to the orbit on the same side. (3) The Pepper type shows a rapid enlargement of the abdomen due to metastases to the liver. These latter types are confined almost entirely to infants.—J. C. D.

A substance which prolongs the life of adrenalectomized cats. Hartman, F. A., C. G. MacArthur and W. E. Hartman, Proc. Soc. Exper. Biol. & Med. **25**: 69-70. 1927.

Nineteen adrenalectomized cats were kept alive for periods ranging from 7 to 60 days by the injection of small amounts of an extract of adrenal cortex. Untreated adrenalectomized animals ordinarily survived only 5 to 6 days. Ox adrenal cortex was extracted with water or 0.8% NaCl. The extract was then cleared of protein and cellular debris by isoelectric precipitation. The substance which the authors name "Cortin" was then obtained by precipitation with NaCl. Epinephrine was removed by washing.

—M. O. L.

Variations of glycogen in heart and brain, and of lactic acid and hexose phosphate in muscles in adrenalectomized rats (Variations du glycogène cardiaque et cérébral, de l'acide lactique et du lactacidogène musculaire chez les rats décapsulés). Houssay, B.

A. and P. Mazzocco, Compt. rend. Soc. de biol. **97**: 1252-1253. 1927.

Fifty-seven decapsulated male white rats and thirty controls were examined six to forty days after operation. In the heart the amount of glycogen was the same in operated and control animals. The cerebral glycogen and the lactic acid in the muscles were somewhat increased in the decapsulated rats. In a number of rats the lumbar cord was cut. When the muscles of a paw were tetanized for one minute, more lactic acid and less hexose phosphate were found in the muscles of the decapsulated animals than in those of the controls. The conditions approximated those of the controls after four minutes rest.—J. C. D.

Output from adrenal anastomosed to the blood vessels of the neck (Décharges d'adrénaline d'une surrénale anastomosée aux vaisseaux du con). Houssay, B. A. and E. A. Molinelli, Compt. rend. Soc. de biol. **97**: 1311-1312. 1927.

The adrenals of one dog were given a blood supply from the carotid and jugular vessels of a second dog. The output of adrenalin was measured by the changes in blood pressure in the second dog. Stimulation of the great splanchnic nerve and injection of nicotine into the blood stream of the donor caused marked output of adrenin.—J. C. D.

The effects of epinephrin on the partition of food stuffs in obese and normal individuals. Krantz, C. I. and J. H. Means, J. Clin. Investigation, **4**: 225-233. 1927.

The data obtained from a study of the respiratory metabolism in seven obese and four normal subjects were analyzed from the standpoint of the effect of injection of 0.625 mgm. of epinephrin on the partition of protein, fat and carbohydrate. In a separate series of cases studied, no significant increase in the protein metabolism was noted after the injection of such small amounts of epinephrin. The protein metabolism was considered to be at a constant level of 15 per cent and after deduction for this the respiratory quotients were interpreted in terms of fat and carbohydrate metabolized. It was found that obese individuals had more fat and less glycogen available for metabolism than did normal individuals. When a metabolic stimulant such as epinephrin was given, the most readily available food stuff was oxidized, and in the case of obese individuals, that was fat.—Authors' Abst.

Noteworthy facts on the actions of adrenalin and carcium on the heart. Murase, H. and K. Nakajima, Journal of Aichi Medical Society, **33**: (6). 1926. Abst., Japan Medical World, **7**: 146.

The authors concluded that up to a certain amount, both adrenalin and carcium accelerated the heart actions of the cold-blooded animals. Both drugs would still further accelerate the heart by the administration of second doses, but if the second dose be too large it either interrupts the heart action or paralyzes it. If carcium was given to the adrenalin paralyzed animals, the accelerating action of the adrenalin became still more marked. It was the same when adrenalin was administered in the carcium paralyzed cases.—R. G. H.

The antagonism between quinine or quinidine and epinephrin. Nelson, E. E., J. Pharmacol. & Exper. Therap. **31**: 209. 1927.

The rise in blood pressure produced by epinephrin or by splanchnic stimulation is diminished after administration of the alkaloids. Rabbit uterus and the retractor penis of the dog are inhibited by epinephrin after these drugs. The author interprets these results as indicating that quinine and quinidine exercise a specific depressant effect on the motor division of the sympathetic nervous system.—C. I. R.

The action of epinephrin upon the cardiac rhythms. Otto, H. L., J. Lab. & Clin. M. **13**: 70-75. 1927.

Since epinephrin by virtue of the powerful accelerator stimulation it induces can cause the appearance of cardiac arrhythmia, in many instances of a dangerous or unpleasant nature, it is distinctly advisable to administer it with caution, particularly to cardiac patients or those individuals presenting a history of having had one of the cardiac arrhythmias.—Author's Abst.

Blood pressure following adrenalectomy. Rogoff, J. M. and R. Dominguez, Am. J. Physiol. **83**: 84-91. 1927.

Blood pressure measurements were made before, during and following adrenalectomy, in dogs, by Van Leersum's (carotid loop) method, which permits observations to be made on non-anaesthetized animals. Nearly all the observations included systolic and diastolic measurements. Observations, made daily, on one dog surviving double adrenalectomy about 12 days and another about 37 days, showed no significant change in blood pressure during the period of good health of the animals. A decided and progressive fall of pressure occurred a few days before death, with the onset of the terminal symptoms. The dog that survived nearly 37 days had the second adrenal removed toward the end of the period of rut.—R. G. H.

The influence of adrenin on the vagus pulse (Der Einfluss des Adrenalins auf den Vaguspuls). Sawitsch, W. W. and E. N. Speranskaja-Stepanowa, Arch. f. d. ges. Physiol. **217**: 413-418. 1927.

Adrenin produces a stronger slowing of the heart-beat the higher the tonus of the heart-center of the vagus nerve, thereby improving the work-capacity of the center. With lowered tone the adrenin action may fail.—A. T. C.

The effects of epinephrin on the auricular tonus waves of the turtle heart. Sollman, T. and T. N. Rossides, J. Pharmacol. & Exper. Therap. **32**: 19. 1927.

Epinephrin abolishes tonus waves and relaxes the tonus of the auricles in three species of turtles. The loss of tonus does not occur if the waves are already absent. With very dilute solutions tonus waves are incompletely suppressed, in which case the rate is decreased, while their amplitude may be increased.—C. I. R.

On the "Calorigenic Action" of epinephrin. Soskin, S., Am. J. Physiol. **83**: 162-170. 1927.

Experiments are reported on 4 normal, 7 eviscerated, 2 hepatectomized and 2 depancreatized dogs. Adrenalin was administered subcutaneously in doses of 0.1 mgm. per kgm. body weight. It was found that epinephrin causes a marked rise in the oxygen consumption and a significant increase in the R. Q. of normal dogs. In eviscerated or hepatectomized dogs, epinephrin does not prevent the usual decline of the oxygen intake, or show any significant influence on the R. Q. In depancreatized dogs, epinephrin causes a definite rise in the oxygen intake, but no significant change in the R. Q. It is concluded that the carbohydrate plethora, caused by epinephrin in the normal dog, is not the essential cause of the increased metabolism which follows its administration. Insulin bears no direct relationship to the calorigenic action of epinephrin. The calorigenic action of epinephrin does not depend on direct stimulation of tissue cells, the presence of the liver being necessary for such an effect.—R. G. H.

A note on the effect of guanidine hydrochloride upon the epinephrin output from the suprarenal gland and the sugar content of blood on dogs. Sugawara, T. and H. Tada, Tohoku J. Exper. Med. **9**: 295-311. 1927.

Guanidine hydrochloride was given intravenously in a dose of 0.15 to 0.3 grams per kgm. of body weight to six dogs, from which the suprarenal vein blood and the ear vein blood (for the blood sugar determination) were collected without fastening, narcotizing or evoking pain. This was made possible by previously cutting the

afferent spinal nerve roots of the operative field. The drug was proved by the results of intestinal segment assays to have accelerated the epinephrin output from the suprarenal gland; five to ten times of the initial discharge was reached. The acceleration began immediately after application of the drug and lasted for several hours at least. After intravenous injection the blood sugar content increased at first. This hyperglycaemia continued half to one and a half hours, then turned to hypoglycaemia, which progressed rapidly.—R. G. H.

Functions of the adrenal cortex and the mechanism of biological oxidations. Szent-Györgyi, A. V., Magy. orv. Arch. **28**: 138-143. 1927. Abst., Chem. Absts. **21**: 2485.

In certain cases of biological oxidations, a hydrogen activation as well as an oxygen activation is required. In the plant the oxygen-activating system has the character of a phenoloxidase, that is, of an enzyme which with the aid of molecular oxygen oxidizes the labile hydrogen of phenol. Also there is present in plant tissues a corresponding aromatic substance which is oxidized by the phenoloxidase to a quinone. This quinone is reduced again by the dehydration system and thus acts catalytically as a hydrogen carrier. In certain plants there is a second aromatic substance acting as a catalyst in the oxidation system. This substance has strong reducing properties. An analogous substance in relatively high concentration was found in the adrenal cortex and appears to form a specific constituent of the interrenal system.

Structural changes in the suprarenal gland of the mouse during pregnancy. Tamura, Y., Brit. J. Exper. Biol. **4**: 81-92. 1926.

Observations made on unilaterally ovariectomized mice during pregnancy showed change in the histological structure of the adrenal. Both adrenals were found to undergo modifications in structure identical with those that occur in the normal pregnant female. There was no correlation seen in the mouse between body weight, body length and the size of the suprarenal gland. The size of this gland did not always indicate its functional activity. During pregnancy the suprarenal became reduced in area. It was noted that hypertrophy of the zona glomerulosa occurs during pregnancy and at the 17 mm. stage it reaches the maximal secretory activity. Hypertrophy of the zona fasiculata may be caused by either an enlargement of cells or an increase in their number. The zona reticularis degenerates rapidly at an early period of pregnancy and at the middle of pregnancy the site of this zone is occupied by vacuoles. The hypertrophy of the medulla occurs at the closing period of pregnancy.—R. C. Moehlig.

Adrenals and solar plexus in anaphylaxis (Le capsule surrenali ed il plesso solare nell' anafilassi). Velardi, F., Folia med. **12**: 452-463. 1926.

By means of vital stains a study was made of the modifications occurring in the adrenals and the solar plexus in rabbits during anaphylaxis. The modifications were of the same order in the two organs.—P. M. N.

Addison's disease, suprarenalopathies, sclerosis of the glands of internal secretion. Wakefield, E. G. and E. E. Smith, Am. J. M. Sc. **174**: 343-357. 1927.

A clinical report of three cases of Addison's disease with a review of the literature. In case I, asthenia, nausea and vomiting with marked bronzing of the skin were the most marked symptoms. At autopsy caseous lesions were found in the suprarenals. With case II there was a series of symptoms simulating Addison's disease but the patient recovered. The authors think that this case was an instance of a toxic or inflammatory suprarenalopathy and not true Addison's disease. The third case was in a person having a familial and congenital pigmentation of the skin, alopecia totalis, and ended not unlike Addison's disease. At autopsy one adrenal was absent and there was a sclerosis of the remaining adrenal. From their own results and from the case reports of others, the authors conclude that the prognosis and treatment are equally discouraging. —E. L.

Simultaneous determination of the blood sugar content and the epinephrin output from the suprarenal gland in the non-anaesthetized, non-fastened dog during peptone poisoning. Watanabé, M., Tohoku J. Exper. Med. **9**: 412-453. 1927.

In the dogs, whose dorsal roots corresponding to the operation field were previously sectioned, the epinephrin liberation from the suprarenal body and the blood sugar content of the ear vein blood were simultaneously determined after an intravenous introduction of peptone in a dose of 0.1 to 0.3 gram per kgm. of body weight. Neither fastening nor anaesthesia was resorted to. The epinephrin liberation began to accelerate with a latency, of half a minute or less, reached its acme in a few minutes, and recovered in a half to two hours or later. The acceleration was from five to thirty times the initial rate in the dogs poisoned moderately or intensively. When too large a quantity of peptone was introduced, collapse developed early and death ensued within a short time; the acceleration was very slight. In general, fluctuation of rate of epinephrin discharge from the suprarenal capsule ran strikingly parallel with the symptoms of shock by peptone. The blood sugar content also fluctuated after peptone. The acme was found one quarter to

one hour after peptone, at about the midst of the depressant stage, and the level decreased then gradually to 0.08-0.05%. The lowest value was found usually two to three hours after injection, and in a further one to two hours the hypoglycaemia disappeared entirely. The moment at which the blood sugar level reached its smallest value was found therefore somewhat later than the recovery of the clinical symptoms as well as of the epinephrin discharge to their normal states. As regards blood sugar fluctuations after peptone, the de-afferented dogs did not differ from normal.

No definite acceleration in the epinephrin liberation on administration of peptone was established by the cava pocket method in experiments under anaesthesia.—R. G. H.

Studies on diabetes insipidus. II. The diuretic substance, preliminary observations. Bourquin, Helen, Am. J. Physiol. **83**: 125-133. 1927.

A substance having diuretic properties has been extracted from sections of the brains of dogs, which were cut in such a way as to include only the mammillary bodies as nearly as that is possible. This substance is present in much larger quantities in the mammillary region of the brains of dogs suffering from experimental diabetes insipidus than in the same region of the brains of normal dogs, and has not been found in extracts of other regions of the brain. It is not precipitated by phosphotungstic acid. A substance having diuretic properties has also been demonstrated in the blood of dogs suffering from experimental diabetes insipidus but not in the blood of normal dogs, which is less active after the preparation has been charred, which is destroyed by prolonged boiling in a weakly alkaline solution, which is relatively stable in neutral solutions and in the dry form, and which is not precipitated by phosphotungstic acid. The substance in the mammillary region and in the blood both cause the same type of diuresis, both cause an excessive response to diuretics injected during the period in which they are acting, and both produce manifestations of thirst. Efforts to detect a similar diuretic substance in the urine have been unsuccessful.—Author's Abst.

Sedimentation velocity of red corpuscles and the effect of various gland extracts (La velocità di sedimentazione dei corpuscoli rossi e suo comportamento in seguito all' azione di estratti ormonici). Corsonello, P., Giorn. di Clin. Med. **8**: 133-141. 1927.

The sedimentation velocity of red corpuscles was studied in the rabbit, according to Gardère's and Lainé's method, before and after treatment of the animals with hypophysis, adrenal, spleen, thyroid and testis extracts. All of the extracts accelerated the total 24-hour sedimentation velocity more than the partial 1- or 2-hour.

—P. M. N.

Notes on the mental development of children exhibiting the somatic signs of puberty praecox. Doe-Kulmann, L. and C. P. Stone, J. Abnorm. Psychol. **22**: 291-324. 1927.

From the data of 62 cases of puberty praecox containing remarks on mental development the following appear to be legitimate deductions: The rate of mental development tends to be normal or subnormal; it is seldom, if ever, really accelerated. Specific trends of mental development are probably not closely correlated with specific types of pathological development or functioning of the endocrine glands underlying the disorder. Such physical traits as height, weight, muscular development, strength, ossification of bones, closure of epiphyseal junctures, and dentition may greatly surpass the norms for children of similar ages, and quite frequently they surpass the extreme ranges for American school children of their respective ages. Precocious development of the external genitals and the secondary sexual characters is usually found, although exceptions to the rule have been described. The extent of precocious development in various elements of the sexual organs of the secondary sex characters is variable from individual to individual. Puberty praecox is considered an acquired disorder arising on a basis of pathological development or pathological functioning of the glands of internal secretion. There is no evidence pointing to a distinctly hereditary basis. A bibliography of 44 citations is appended.—Author's Abst.

Functional relation between endocrine glands and fracture of bones (Rapporti funzionali tra ghiandole endocrine e frattura occea). Enriquez, P. and L. Robuschi, Arch. di fisiol. **24**: 382-447. 1926.

Following fractures of bones the thymus was found to increase in size; many thymocytes became unicellular Hassal corpuscles, and then pluricellular ones. The old pluricellular ones (true reservoirs of secretion) rapidly completed their secretory cycle. When the fracture was almost healed the thymus decreased to even less than its previous size. Injection either of fractured bones or of calcium salts may induce similar reaction from the thymus. The reaction of thymus to fracture was more accentuated in adult animals than in the very young ones. The anterior portion of hypophysis similarly reacted to fracture of bones, assuming again a foetal character. Injection of calcium salts gave the same peculiar coloration obtained after fracture.—G. V.

Some results of endocrine therapy in behavior disorders of children: A preliminary report. Geiger, Sara, Tr. Chicago Neurological Society, Abst., Arch. Neurol. and Psychiat. **18**: 1050. April 21, 1927.

Twenty children showing evidences of glandular imbalance,

who were referred to the Institute for Juvenile Research on account of behavior disturbances involving poor judgment, restlessness, lack of concentration and difficulties arising from mental deficiency or a feeling of inferiority were treated with gland extracts. These children have been studied, usually at weekly intervals, over periods ranging from six to thirty months, to determine the effect of the treatment on mentality, physique and behavior. Pituitary substance given by mouth produced no change either in the physical condition or in behavior. An attempt was not made to elevate a low metabolic rate above a high normal plus rating; with the dose of thyroid sufficient to do this, loss of body weight did not occur; however, the emotional reactions became more stable. Pituitary extract given hypodermically in increasing doses produced no change in physique; however, the children with mental defect became less restless and were not so definitely alien in a normal social group. A carefully selected diet, low in carbohydrates and fats, alone or in any combination with the aforementioned substances, produced a diminution in weight, which occurred more promptly in combination with thyroid substance. Pituitary extract administered hypodermically and thyroid substance administered orally, singly or combined, produced definite changes in behavior consisting of less sullenness, less restlessness, more stable emotions, and better concentration, leading to improved adjustments in home, school and play. The results secured indicate that there are advantages in endocrine therapy. Further data, including laboratory observations, roentgenographic study of bone browth, visual fields, growth curves, statistical data and the relation of sex problems to endocrine pathology are in course of preparation.

Some experimental and clinical facts concerning follicular hormone (Quelques faits experimentaux et cliniques concernant l'hormone folliculaire). Brouha, L. and H. Simonnet, Presse méd. **103**: 1619. 1926.

The earlier experimental work on the follicular hormone is reviewed. The author concludes that the term "folliculine' used by Courrier is the one of choice. The method of preparation of the hormone is briefly outlined. The clinical observations reported are five cases of amenorrhea, one case of dysmenorrhea, and one of hypoplasia of the uterus and dysmenorrhea, and two of menopause. The return of menstruation following a varying period of amenorrhea was credited by the author to the influence of the hormone. He concludes that in a certain number of cases of ovarian hypofunction and in disturbances of the menopause, the use of folliculine has given satisfactory results. It is a question whether this is due to direct action on the genital tract or to some influence on the ovary. Certain peculiarities in the responses, such as the ad-

vance of the date of menstruation or the appearance of menstruation following a single injection suggests that folliculine plays an active rôle in the process of menstruation. The clinical use partially confirms the experimental results attributed to the hormone. Observations are in progress as to whether this will substitute for the ovaries in cases of castration at operation.—J. P. Pratt.

The relation between menstruation and ovulation in the monkey. Corner, G. W., J. Am. M. Ass. **89**: 1838-1840. 1927.

From data secured at autopsy and by exploratory operation in young mature females of the monkey, Pithecus (Macacus) rhesus, it was seen that menstruation frequently occurs without detectable evidence of ovulation, and is therefore apparently not dependent on the presence of a corpus luteum. However, when ovulation occurs, it seems to take place at a definite time, about twelve or fourteen days before the onset of menstruation. Menstruation without ovulation is not preceded by the so-called premenstrual changes of the endometrium, which occur only after formation of the corpus luteum. The cause and meaning of menstruation, in this species, are not at present known. Physicians in a position to obtain human material are urged to gather and study it in the light of these new facts discovered in a related species.—R. G. H.

Ovarian hormone in water soluble form. Dickens, F., E. C. Dodds and D. J. T. Brinkworth, Lancet, **212**: (i) 1015-1016. 1927.

A method of obtaining oestrus-producing hormone in water soluble form from placenta is outlined. The essential steps consist of treatment with hot 7% hydrochloric acid, adjustment of the pH to 3, passage through a Sharple centrifuge, and successive treatment with saturated picric acid, acid alcohol and acetone. This method yields 1,000 rat units per kgm. of placenta, the rat unit being 0.5 mgm. of the product.—E. A.

Observations on the activity and working power of the uterine muscle of the non-pregnant sow. King, Jessie L., Am. J. Physiol. **81**: 725-737. 1927.

Observations on the isolated muscle of the pig's uterus in 70 animals indicate that the circular and longitudinal layers function differently and that both pass through significant changes in activity and in working power (53 specimens) during the oestrous cycle. The work accomplished is greatest during oestrous and least at the time when the corpora lutea are at the height of development.

—R. G. H.

Studies on vigor. XI. Relation of hysterectomy to voluntary activity in the white rat. Durrant, E. P., Am. J. Physiol. **82**: 14-18. 1927.

In an experiment with 26 hysterectomized and 6 control white rats observations were made by means of vaginal smears and by recording voluntary activity. The results indicate that the uterus exerts no hormonal effect on the cyclic activity of the ovary. Our observations, carried out by the revolving cage, confirm the results of the work of Long and Evans by the vaginal smear method.

Author's Abst.

True hermaphroditism in man. Kwartin, B. and J. A. Hyams, J. Urol. **18**: 363-383. 1927.

A negro, 24 years old, showed externally hypospadius, a mass in the right inguinal canal, but no right testis. Internally there was a small uterus opening into the urethra. The left gonad was in the position of an ovary, but was an ovotestis, as sections showed. This is the eleventh case of true human hermaphroditism reported. There is a brief discussion and a list of 55 references.—J. C. D.

A note on the preparation and properties of a female sexual hormone (menformon) in water-soluble form. Laqueur, E., P. C. Hart and S. E. de Jongh, Lancet **212**: 1126. 1927.

A resume of the authors' methods of preparation of a water soluble product of a high degree of purification.—E. A.

The feminizing influence of the female sex hormone (menformon) on the undeveloped mammary gland. Laqueur, E., S. E. de Jongh and M. Tausk. Deutsche med. Wchnschr. **53**: 867. 1927.

Injections of "menformon" over long periods (3 weeks to 4 and 5 months) stimulated growth of the secretory parts of the mammae in immature rats of both sexes and also in mature male rats. This mammary growth influence is considered specific for the "female sex hormone."—E. A.

On a peculiar type of intersexuality in the guinea-pig. Lipschütz, A., Brit. J. Exper. Biol. **4**: 227-244. 1927.

An abnormality of the external genital organs in 16 otherwise normal female guinea-pigs is described. Fifteen of these animals were from Estonia, one from Riga in Latvija. There were an hypertrophied penis-like clitoris and horny styles similar to those in the intromittent sac of the normal male penis. The length of the hypertrophied clitoris and of the horny styles varied much. The greatest length of the external part of the clitoris was 4 mm.; the greatest length of the horny styles was 3½ mm. The abnormalities were often asymmetrical, the clitoris and the horny styles on one side being more developed than on the other. They may even be absent on one side. The abnormal conditions of the external genital organs in these animals are identical with those described for the

castrated female guinea-pig, experimentally masculinized by testicular transplantation. It is suggested that the malformation is a peculiar type "of partial somatic intersexuality," according to the classification as given formerly by the author. This suggestion is based on the consideration that whereas the external genital organs resembled those in the male guinea-pig, there was no indication of the ovaries being abnormal or producing simultaneously female and male sexual hormones. The ovaries of the abnormal females when grafted into castrated males produced the typical female hormonic effect on the mammary glands as normal ovaries do; the engrafted ovaries of the abnormal females had no influence on the penis or on the horny styles of castrated males. The clitoris and the horny styles of the intersexual females were not affected by removal of the ovaries, whereas in the male removal of the testes causes a pronounced regression of the horny styles even in fully grown animals; the horny styles when cut regenerated; they did even after removal of the ovaries; on the contrary, there is never a regeneration in the castrated male, but only in the normal male.
—Author's Abst.

Ovarian secretion and tumor incidence. Murray, W. S., Science, **66**: 600-601. 1927.

Non-breeding reduces tumor incidence in mice and delays the time of tumor appearance (207 mice used). Two hundred and ten female mice, castrated at 28-35 days, behaved much the same as non-breeding females. Two hundred and forty-one males castrated at 28-35 days did not develop tumor, thus resembling non-castrated males. Spontaneous tumors, never obtained in thousands of normal males of the stock used, may develop in castrated males which have received subcutaneous transplants of ovarian tissue (210 operated—four tumors).—Author's Abst.

On the occurrence of the oestrus cycle after x-ray sterilization. Part IV. Irridation of the adult during pregnancy and lactation; and general summary. Parkes, A. S., Proc. Roy. Soc. B. **102**: 51-62. 1927.

A paper containing five tables regarding the effect of x-rays on lactation, oestrus cycles and pregnancies. A summary of the author's previous work is also included in this paper. From his results the author drew the following conclusions: Irradiation during early pregnancy causes reabsorption or abortion of the feti. During lactation the follicular disintegration produced does not affect the persistent copora lutea of lactation. When the young females were irradiated the ova degenerated, but on the attainment of sexual maturity the normal cyclic changes were found in the accessory organs. The only exceptions were found in the animals in which the ovaries had undergone luteal degeneration. This destruction of

the Graafian follicle shows that the oestrus cycle is not dependent on the alternate maturation of the follicle and corpus luteum.—E. L.

The experimental bases for the theory of sex differentials. (La notion des "Seuils differentiels" sa base experimentale; son importance en endocrinology sexuelle.) Pezard, A., Rev. franç. d'Endocrinol. **4**: 233-253. 1927.

The author reaffirms his previously reported idea of sex thresholds, and produces the four following "laws," based upon experimental data secured by a study of the relation of the testes to the comb of the cock, to support his case: Law of definite equilibrium is based upon the observation that four grams of testicular tissue form a neutral zone. Law of the rate of development indicates the development rate is independent of the mass if above four grams. Law of the rate of regression holds that the regression curve is the same in total castration and partial castration if the remaining mass is less than four grams. The law of angular discontinuity is based upon the observation that if, either through regeneration or graft, the testicular mass of a previously castrated animal reaches a value of more than four grams, regression ceases and growth begins. The angle in both cases coincides provided the testicular mass exceeds four grams. From these observations it is concluded that four grams is the threshold value for the comb, and that the action is an "all or none" reaction. To determine whether the other sex characters, such as sex instinct and crowing, had different thresholds, various degrees of incomplete castration were produced. The result made it possible to determine four well differentiated groups. Three of the sets of factors were produced by 4-6 grams of testicular tissue, the fourth only on an excess above this. The author believes that the substance for each action is the same qualitatively and the varying action is produced by different quantities. A number of difficult questions, such as gynandromorphism in chickens, are explained on the above hypothesis.—Bert Cunningham.

Monkey testicle grafted in man. Retterer, E., J. d'urol. méd. et chir. **24**: 97-115. 1927. Abst., J. Am. M. Ass. **89**. 1909.

A lawyer, aged 66 years, found that his memory was getting poor and that he became fatigued after two hours' work. He had been impotent for two years. Three months after implantation of a monkey testicle (Cynocephalus sphinx), his intellect, especially his memory, was greatly improved, as well as his endurance. His genital functions returned, but after twenty-eight months were decreased by one-half. Although the intellect maintained its improvement, he requested a new graft. Retterer examined the old graft and concluded that the element producing the stimulating principles is the epithelium of the seminiferous tubules; general well-being

lasts from three to four years; that is, until sufficient time has elapsed for the transformation of the epithelial covering into connective tissue.

Studies on the physiology of reproduction in birds. XXII. Blood fat and phosphorus in the sexes and their variations in the reproductive cycle. Riddle, O. and Frances H. Burns, Am. J. Physiol. **81**: 711-723. 1927.

During the ovulation cycle of female ring-doves the amount of alcohol-ether-soluble substance in the whole blood is increased to 35% above the normal or "resting" value. The phosphorus contained in this extract is increased to approximately 50% above the normal value. This well-marked cyclic increase in the fat and lipoid phosphorus of the blood recurs with each ovulation period. In female doves forced to continuous egg-production the metabolism of fat and phosphorus is therefore repeatedly brought to and temporarily maintained at an unusual level. The literature on changes in blood fat and phosphorus in the reproductive cycle in animals and man is reviewed. Cyclic changes earlier observed in these doves —suprarenal hypertrophy, increased blood sugar, increased blood calcium—all reached a maximum coincident with the "ovulation period." The blood fat and phosphorus, however, attain their maximum 67 to 45 hours earlier—in the pre-ovulation stage of the cycle. Because of the known relations of the ovary to fat metabolism this earlier maximum of fat suggests that the ovary itself—rather than suprarenals or parathyroids—is more directly responsible for the entire series of changes hitherto observed in the reproductive cycle. Considered as groups, normal male ring-doves have less blood fat (1.77 g. per 100 cc.) than normal females (2.02 g.) in the "resting stage" or in any other stage of the reproductive cycle. An increased storage of fat earlier found by Riddle to characterize the female-producing ova of pigeons is thus paralleled by a higher concentration of fat in the blood of adult females. The literature dealing with blood fat as a sex-differential is reviewed. From the protozoa to man there is meagre but uncontradictory evidence that the metabolism of fat is not equal in male and female. This inequality is probably not to be regarded as a secondary sex character, but as a direct expression of the metabolic difference which one of us has earlier identified with primary sex difference.—Author's Summary.

Ovarian follicular hormone in blood of pregnant women. Smith, M. G., Johns Hopkins Hosp. Bull. **41**: 62. 1927.

A substance identical in its biological reactions to ovarian and placental hormone is present in the blood of pregnant women. Its concentration increases from the second month to the termination of pregnancy, being highest just before and during labor. There is a rapid disappearance from the blood following delivery. It can

be demonstrated in the urine just before and following labor. The amount in the placenta per gram weight is approximately twice that in the blood per cubic centimeter. The concentration in maternal blood during labor and in blood from the umbilical cord is the same.—E. A.

Ovarian hormone. Truffi, G., Arch. di Scienze Biol. **10**: 147. 1927. Abst., J. Am. M. Ass. **89**: 2148.

In his experiments Truffi used the follicular fluid of mares. A single subcutaneous injection (from 3 to 4 cc.) brought about the development of pre-oestrual phenomena and oestrus in female guinea-pigs, rabbits and dogs—immature as well as sexually mature. Such phenomena regress when treatment stops. If treatment is extended to twenty or forty days, the oestrual phenomena are also prolonged. In sexually mature animals, even if castrated, typical phenomena develop, such as normally appear only in the presence of corpus luteum. In immature animals, maturity is hastened and secondary sex characteristics are influenced. Liquor folliculi may thus replace both corpus luteum and interstitial gland. The ovarian epithelial element may exercise its specific hormone action without reaching the lipoid element stage. In male animals follicular fluid exerts an evident antitesticular and antimasculine effect. In the guinea-pig it stops spermatogenesis and promotes the growth of the mammary gland, and in the cock it influences the growth of the comb. In order to cause such changes, it must contain the specific ovarian hormone. This hormone has a physiologic and sexual but not a species specificity.

Protracted oestrus induced by ovarian extracts. Tuisk, R., J. Physiol. **63**: 180-186. 1927.

Extracts of follicular fluid were injected into normal and castrated mice for periods varying from 8 to 16 days. Oestrus cornification of the vaginal epithelium continued for 7 days in castrated and 13 days in normal animals. The conclusion drawn is that continuous oestrus results when a threshold concentration of hormone is maintained.—E. A.

The relationship between insulin and the ovaries and its therapeutic value in the treatment of uterine hemorrhage (Uber Beziehungen zwischen Insulin und Ovarium und ihre therapeutische Verwertung bei der Behandlung von Uterusbluntungen). Vogt, E., Zentralb. f. Gynäk. **51**: 719-735. 1927.

Vogt discusses the function and action of insulin. He also discusses at length its relationship to the general endocrine system, to the vegetative nervous system, and to the ovaries. He has used insulin with apparent benefit in the treatment of various forms of pathological uterine hemorrhage. Insulin influences the internal

secretion of the ovary and thereby affects the entire endocrine system. It also affects the duration and amount of menstruation, by reducing the hyperglycemia of menstruation. The action of insulin upon the ovaries shows the inter-relationship between the hormones, the vegetative nervous system, and the ionic content of the blood.
—J. P. Pratt.

The effect of ovarian traumatization on the spontaneous activity and genital tract of the albino rat, correlated with a histological study of the ovaries. Wang, G. H. and A. F. Guttmacher, Am. J. Physiol. **82**: 335-349. 1927.

Experiments were performed on the white rat to ascertain the changes in the activity and the vaginal smears after experimental ovarian traumatization, and the correlation of these changes with the histological structure of the traumatized ovaries. Out of 28 animals, 8 showed no change in either the activity, the vaginal smears, or the cellular structure of the ovary; 4 showed castrate effects in both the activity and the vaginal smears and complete degeneration of the ovaries; 15 (53%) showed changes in both the activity and the vaginal smears; and one showed smear changes with a castrate level of activity. The change in activity was expressed in the disappearance of the normal four-day oestrous rhythm, despite the maintenance of the pre-operative daily running averages. In the vaginal smears, the normal four-day cyclic variations in cellular contents also disappeared, and only cornified epithelial cells were consistently observed. The uterus showed great hypertrophy. These changes in the activity and the vaginal smears lasted until either the traumatized ovary was removed or the animal killed. We have observed them from 40 to 170 days after the traumatization operation was performed. After the injured ovary had been removed, the usual castration effects on both the activity and the accessory sexual organs were obtained. It is the secretion from the follicular cysts which is responsible for the changes in both the activity and the accessory sexual organs found in rats whose ovaries have been moderately traumatized, since these cysts were the only structures consistently found in the injured ovaries of these animals. The only cellular element constantly present in the follicular cysts was the granulosa layer. Thus, the granulosa cells may have given out the hormone which produced increased activity, cornification in the vaginal epithelium, and hypertrophy of the uterine wall. In one animal consistent cornification of the vaginal epithelium and uterine hypertrophy were found with low arrythmic activity, and its ovary contained neither follicular cysts nor large Graafian follicles, but only corpora lutea.—Authors' Abst.

The hormone of the heart-beat (Ueber ein Hormon der Herzbewegung). Haberlandt, L., Arch. f. d. ges. Physiol. **216**: 778-788; 789-795. 1927.

Further evidence is presented of a specific hormone controlling the heart-beat.—A. T. C.

Raynaud's disease and the pituitary (Raynaudsche Krankheit und Hypophyse). Bloch, E., Klin. Wchnschr. **6**: 457-459. 1927.

Bloch reports a case of a woman, aged 59, with scanty menstruation every 4 weeks and of one day duration. The menopause occurred at 53 years. There was swelling of the face and hands as well as fatigue and loss of memory. A diagnosis of myxedema was made in 1919 and she was then treated with thyroid. There was a rapid improvement in her condition. She received thyroid for 5 years and was then given ovarian tablets. In 1924 the beginning of Raynaud's symptoms were confined entirely to the fingers. There was marked anemia of the fingers during cold weather; thickening of end phalanges with severe pain and asphyxia. In 1925 these attacks were uninfluenced by the weather. There were at that time marked trophic changes as well as excessive thirst and crumbling of the teeth. The patient was treated with hypophysis tablets, after which disappearance of thirst and teeth symptoms was noted. There was no change in Raynaud's symptoms. The author believes that every case of Raynaud's disease should receive pituitary injections, as other therapy is quite hopeless. Without detracting from the theoretical basis of the therapy, his evidence for pituitary involvement in this particular case is not very strong; basing it as he does on the fact that the patient had thirst and teeth involvement which were benefited by pituitary tablets by mouth.

—R. C. Moehlig.

Dosage and action of pituitary extract and of ergot alkaloids on uterus in labor. Action of epinephrine. Bourne, A. and G. H. Burn, J. Obst. & Gynec. Brit. Emp. **34**: 249. 1927.

Bourne and Burn have studied the changes taking place in the human uterus after the administration of pituitary extract and the separate ergot alkaloids, trying to find whether the minimum dose was without danger at any stage of labor. They introduced into the uterus a rubber bag which was connected by rubber tubing to a mercury manometer. The variations in the level of the mercury were recorded by a float bearing a celluloid flag, on the end of which was an ink writing point. After the bag had been introduced and the record started, they watched the succession of uterine contractions during a period from 45 to 50 minutes. During the first 15 to 20 minutes there was usually an increase in contraction, due in part to the stimulating effect of the bag, and in part to the passing away of the inhibitory effect of the anaesthetic, as the last traces were exhaled. The tracings of contractions remained approximately regular in size during the next 30 to 40 minutes before the pituitary extract was injected. In thirteen cases studied with pitui-

trin extract it was found that two units seemed to have a valuable effect, not so much in providing a powerful stimulus to strong expulsive uterine contractions, but in regularizing such contractions and perhaps in producing co-ordination between fundal contraction and the cervical inhibition or relaxation. They came to the conclusion that a small dose of pituitary extract may be expected to produce an effect which should be useful in hastening the course of a sluggish labor, provided that it is not administered before the os is about one-half dilated. A dose of two units may be given with safety at any stage, provided there is no mechanical obstruction. They studied the action of the separate ergot alkaloids in the same way as pituitrin was studied. They found that tyramine has no value in obstetrics. Histamine in a dose of 2.0 mgms., when injected under the skin, produces a powerful but short lived effect. It appeared to exhaust the uterine activity. The specific alkaloid of ergot (ergotamine or ergotoxin) exerts a very powerful action and appeared to be an ideal agent for use after delivery. The fluid extract of ergot (British Pharmacopae) does not contain the specific alkaloid, and in view of the results they obtained it can have no therapeutic effect. They also determined that adrenalin injected into the vein inhibits uterine contraction before delivery. The administration of ether has a similar effect.—J. P. Pratt.

Studies in acromegaly. VI. The disturbances of carbohydrate metabolism. Davidoff, L. M. and H. Cushing, Arch. Int. Med. **39**: 751-786. 1927.

The authors have studied a series of 100 cases of acromegaly, with special reference to carbohydrate metabolism. In this series they have found one case out of four to have glycosuria and approximately one case out of eight to have diabetes mellitus. They discuss in detail the etiology of this glycosuria. A type of adenoma, composed of chromophil cells, and accompanying acromegaly, is mentioned as the one type of tumor which is prone to cause a disturbance of sugar metabolism. The inter-relation of the pancreatic and hypophyseal secretions is also discussed, with many references to the literature. It is concluded that the pancreas and its islet tissue exerts a reciprocal effect on the hypophysis; that both pancreatic islets and hypophysis have some influence on sugar metabolism; that insulin serves to affect favorably both acromegalic and pancreatic forms of the disease; and that a hypophysectomy may offset experimentally produced diabetes. Sugar tolerance tests were also made on several patients with acromegaly, but without glycosuria. All of these were found to have a decreased tolerance for sugar. Again, in a series of six cases in which partial hypophysectomy was performed, four of the cases showed a distinct improvement in the sugar tolerance after the operation. The authors finally conclude that the glycosurias accompanying acromegaly can be ascribed

to the hyperpituitarism because: patients with acromegaly, even in the absence of glycosuria, usually have a low sugar tolerance and some hyperglycemia, whereas patients with hypopituitarism usually have a high tolerance for sugar and show hypoglycemia. The melituria of acromegaly may be recovered from spontaneously, which is seldom if ever true of pancreatic diabetes. Insulin and posterior lobe extracts have been shown to be, and insulin and anterior lobe extracts may be presumed to be, counter-active in their effects. Insulin will control acromegalic diabetes, but far less effectively than it does the more common forms of diabetes unassociated with hyperpituitarism, the assumption being that the increased pituitary activity tends to counteract its effects. The partial extirpation of the acromegalic adenoma will apparently render patients with diabetes more amenable to insulin, and may promptly lower the tendency to hyperglycemia exhibited by many of these patients even in the absence of active glycosuria.—H. M. Keith.

Studies in the causes of dental anomalies. Downs, W. G., Genetics, **12**: 570-580. 1927.

Six hundred and forty-seven patients were studied. Some were taken from a hospital for the insane, others from a school for feeble-minded, and still others from private clinical cases. Two hundred and twenty-nine were normal and four hundred and eighteen showed bodily deviations more or less definitely ascribable to endocrine factors. In short, about 50% of cases of endocrine dyscrasia showed dental anomalies as contrasted with 17% in the normal subjects. Experiments were made with feeding and injecting dogs with the extracts of both the anterior and posterior lobes of the pituitary gland. Five puppies about one month old were fed extracts of anterior lobe, five were fed posterior lobe and five others were given the whole gland. Five were kept as controls. Litter mates were used in each case. When the animals were killed by litters at intervals of 4 to 8 weeks, no influence on dental conditions could be detected. Similarly negative results were obtained in 6 cases of "antuitrin" and 6 of "pituitrin" injections. A rather marked hereditary trend in dental anomalies was found in the human subjects.—R. G. H.

Hypopituitarism: A summary of observations in twenty-seven cases followed seven years. Eidelsberg, J., J. Am. M. Ass. 89: 449. 1927.

Fourteen of the 27 patients were distinctly below the average normal height for their age and sex. Fifteen were females of whom 8 had never menstruated. Of the 7 other females, 4 gave history of irregularity and scantiness, and 2 of these are practically normal at the present date. Twelve were male patients, and 6 of these

had no hair over the pubes, in the axillae or on the face. Desiccated whole gland pituitary substance was administered in doses of 1 to 5 grains daily. The greatest improvements and the greatest disappointments occurred with regard to obesity. The average loss of weight was 32 pounds. The average increase in height was 4½ inches. In 12 of the 27 patients, headache was an important symptom. Of the 27 patients, 11 had blood pressure varying between 86 and 100 systolic. The best results from all angles, such as growth and weight, were obtained in the younger patients, those under 20 years of age. The best results were obtained with the larger doses of the whole gland, from 50 to 75 grains (3.25 to 5 gm.) daily. Persistency and patience in the treatment were found to be very important.—R. G. H.

Is cutis verticis gyrata a symptom in an endocrine syndrome which has so far received little attention? Grönberg, A., Acta med. Scandinav. **77**: 24-41. 1927.

A case of cutis verticus gyrata in which acromegalic symptoms were also present, is described. Nine other cases, with acromegalic symptoms, are reviewed from the literature. Although no enlargement of the sella turcica was observed in any case, the author believes that a functional disturbance in the pituitary is responsible.

—M. O. L.

The effect of pituitrin administration upon the distribution of injected fluid. Hines, H. M., C. E. Leese and H. R. Jacobs, Am. J. Physiol. **83**: 269-274. 1927.

Pituitrin was added to Ringer's solution and administered by the continuous intravenous method to 10 unanesthetized dogs. It exerted no effect on the volume output of urine during the period of injection (usually a two-hour period). It caused a much greater blood dilution and a decreased rate of removal of the injected fluid by the tissues. Its administration was followed by a greater urine output in the three-hour post-injection period. The authors believe that this increased urine output represents primarily the elimination of the extra fluid from the blood stream, during the time of abating pituitrin action, rather than diuretic action of pituitrin per se. When injections of pituitrin and Ringer's solution were made in dogs under ether anesthesia only, a slight dilution of the blood was noted. The volume of urine excreted during the injection period was, on the average, somewhat increased. The quantity of fluid calculated to have been taken up by tissues exceeded that found in experiments on the unanesthetized animal with either Ringer's solution alone or Ringer's and pituitrin.—R. G. H.

The role of the pars intermedia in the regeneration of batracians urodeles. (Le rôle du milieu intérieur dans la régénération des

Batraciens urodèles). Schotté, O., Compt. rend. Soc. de biol. **94:** (6) 1177-1179. 1926.

Schotté has reported that adult tritons and salamander larvae showed either total arrest or considerable retarding of regeneration in every case in which hypophysectomy was complete. However, the same operation has not exerted any noticeable influence on the regeneration of 45 triton larvae. Quoting several American and European authors, he says this may be understood from a reciprocal action between the thyroid and hypophysis, the thyroid substituting for the hypophysis and vice versa. Schotté agrees with Guyénot that the organism is a mosaic of regions having their own regenerative powers and losing them independently of each other. But for these regenerative powers to manifest themselves the presence of certain conditions is necessary, two of which seem to play quite a basic rôle: the sympathetic nervous system, of which he has succeeded in showing the importance, and the hormonic constitution of the pars intermedia regulated principally by two glands, the hypophysis and the thyroid.—R. C. Moehlig.

Diabetic acidosis and leucocytosis. Allan, F. N., Am. J. M. Sc. **174:** 506-510. 1927.

Five cases of diabetic acidosis in which the symptoms simulated acute intraäbdominal lesions were presented. The nausea and vomiting, as well as the leukocytosis, was misleading. The leukocytes in the absence of infection varied from 16,000-28,000. With the disappearance of the acidosis, due to treatment, the leukocytes returned to the normal level.—E. L.

Concerning the effect of cobalt on insulin hypoglycemia in rabbits. Blatherwick, N. R. and M. Sahyun, Am. J. Physiol. **81:** 560-562. 1927.

Bertrand and Mâcheboeuf reported experiments on rabbits which led them to conclude that small additions of either cobalt or nickel enhanced the hypoglycemia produced by insulin. Similar experiments with cobalt have been repeated by the authors of this paper. Using standardized rabbits, no evidence for the belief that this element causes a greater hypoglycemia was obtained. The insulin was given both intravenously and subcutaneously. The favorable results of the original investigators are believed to have resulted from individual variations in the animals used.—Authors' Abst.

Course and prognosis of diabetes mellitus in children. Boyd, Gladys L., Canad. M. A. J. **17:** 1167-1172. 1927.

A study of 95 patients under 15 years of age treated at the Hospital for Sick Children, Toronto, between 1918 and 1927, has led to the following conclusions: The average length of life of diabetic

children has been lengthened by insulin treatment, under which normal growth and development occur. The criterion of successful treatment consists of absence of glycosuria and maintenance of normal blood sugar for the greater part of the time. Fluctuations in tolerance are found to be frequent. Certain pathological evidence favors the belief that pancreatic regeneration may occur. The incidence of diabetic coma has not lessened, but its mortality has materially decreased, due on the one hand to insulin treatment, and on the other to earlier recognition and treatment.—A. T. C.

Synthalin in diabetes. Carrasco-Formiguera, R., Rev. méd de Barcelona, **7**: 246. 1927. Abst., J. Am. M. Ass. **89**: 413.

The author was perhaps the first physician outside of Germany who had the opportunity to try synthalin. He confirms previous reports to the effect that the chief advantage of the new drug lies in its ability to act when administered by mouth. On the other hand, its toxicity may cause disturbances and its slow action precludes its use in emergencies. Cases refractory to insulin will probably be even more refractory to synthalin. At best, it is but a partial substitute for insulin in moderate and severe cases. In mild diabetes it can prove, however very useful.

Insulin reactions. Foshay, L., Arch. Int. Med. **40**: 661-667. 1927.

The previous studies of insulin reactions have not been fruitful, because the only method of analysis has been a study of the whole blood sugar. A study of the recorded data shows that the occurrence of insulin reactions bears no direct fundamental relation to the whole blood sugar concentration. In a few diabetic patients, as in experimental diabetes in dogs, it was found that the insulin reaction is seen only when the sugar content of the blood corpuscles is low. The corpuscular glucose concentration may be accepted as an index of the glucose concentration in the cells of the fixed tissues, hence the fundamental cause of the symptoms and signs of insulin reactions is believed to be a lack of available glucose throughout the tissue cells of the body. By a determination of corpuscle sugar many impending reactions may be recognized early and completely prevented by proper prophylactic treatment. This method is especially valuable for the study of patients who are in coma, for at that time the symptoms are lacking and the physical signs may be obscured.—R. G. H.

A synthetic substance (synthalin) with insulin action. Frank, E., Naturwissenschaften, **15**: 213-215. 1927. Abst., Chem. Absts. **21**: 2320.

Guanidine subcutaneously injected (0.3 gram per kgm. body weight) gives in a starved rabbit progressive hypoglucemia and

convulsions, 0.035 to 0.05% blood sugar after 4 hours. Subsequent feeding of glucose cannot prevent this action. The derivative agmatine (aminobutyleneguanidine) from herring sperm, synthetically prepared, 0.08 to 0.1 gram per kgm., lowers the blood sugar over 30% without visible symptoms. Larger doses give an initial hyperglucemia followed by hypoglucemia and convulsions. For aminopentuleneguanidine (one more methylene group) the intermediary stage is absent; it has an effect parallel to that of insulin. The blood sugar goes down to 0.05% and convulsions appear (0.2 gram per kgm.); a few drops of glucose solution given intravenously restore the normal condition. To increase further the hypoglucemic action lengthening of the CH_2 chain is favorable, and also a second structural change (not divulged). A preparation C has been thus prepared of a convulsion dose of 0.003 gram per kgm. rabbit. This produce (synthalin is its HCl salt) acts favorably on diabetic dogs; it can be fed per os. For human consumption a dose of 20 to 25 mgm. is given per os, maximal in 4 days 125 to 150 mgm.; it makes the metabolism of 40 to 50 grams glucose per day possible. Of the synthalin, 1 mgm. is approximately equivalent to 1 insulin unit; crystalline insulin is 75 to 100 times more active than the free base of synthalin. More than 160 cases have been treated.

The effect of insulin on hypophysectomized dogs. Geiling, E. M. K., D. Campbell and Y. Ishikawa, J. Pharmacol & Exper. Therap. **31**: 247. 1927.

An investigation was made of the response to insulin by completely or partially hypophysectomized dogs, also of those in which escape of the posterior lobe secretion was interfered with by various means. Such animals were found to become increasingly hypersensitive to insulin, as manifested by hypoglycemia, salivation and convulsions. The anterior lobe does not seem to be involved. Extracts of the posterior lobe in large doses will protect against both hypoglycemia and convulsions, but in small doses protect only against convulsions. The authors suggest that the pituitary as well as the thyroid is involved in the production of the variable response of normal animals to insulin.—C. I. R.

Diabetes mellitus. Glassberg, B. Y., M. Somogyi and A. E. Taussig, Arch. Int. Med. **40**: 676-685. 1927.

A case of diabetes mellitus is reported which showed the following peculiarities: Beginning as a mild case, it rapidly became more severe and at one time showed an allergic reaction to insulin. For a period of some months the patient proved relatively refractory to insulin, responded only to enormous doses of insulin and slipped into coma or precoma as soon as these doses were reduced. During this period the patient did not respond better to fractional

doses of insulin than to an equivalent single dose: on the whole, the latter was more effective than the former. In ordinary diabetes the reverse is true. To a moderate degree, the patient's response to insulin seemed to be increased by the simultaneous injection of parathyroid extract. Later, the response to insulin increased, and the case again became an ordinary, moderately severe diabetes. It is shown that the patient's failure to respond in the usual manner to insulin can be explained neither by a destruction of insulin in the body nor by its excretion in the urine. It is suggested that in this case, as perhaps in other similar ones reported in the past few years, the diabetes was due not only to a lack of pancreatic secretion, but also to a lack of muscle enzyme (phosphates, insulin complement, glycomutin).—Authors' Abst.

The initial hyperglucemic effect of insulin. Guardabassi, M., Ann. fac. med. chir. **29**: 147-177. 1927. Abst., Chem. Absts. **21**: 3963.

A transient hyperglucemia is caused by subcutaneous, and more distinctly by intraperitoneal, insulin injections. It is absent or very slight in thyroidectomized animals, while thyroid feeding exacerbates both hyper- and hypo-glucemia and the toxic effect. Adrenal disease or adrenalectomy has no effect. The hyperglucemia is pronounced in diabetics and absent in castrated animals, although the latter are highly sensitive to insulin. The data are followed by a lengthy discussion on the influence of the various hormones through the medium of the liver.

Experiments on phloridzin glucosuria. VII. Metabolism in phloridzin diabetes on an unbalanced protein diet (Untersuchungen über die Phlorrhizinglucosurie. VII. Das Stoffwechselgeschehen im Phlorrhizin-Diabetes bei einseitiger Ernährung mit Eiweiss). Hanisch, Sofie and P. Junkersdorf, Arch. f. d. ges. Physiol. **217**: 264-278. 1927.

Provided excess of protein is fed the characteristic hypoglucemia and fatty infiltration of the liver are not produced.—A. T. C.

Studies concerning the influence of potassium iodide and thyroid preparations upon the blood sugar curve. Holsti, Ö., Acta med. Scandinav. **66**: (45) 461-466. 1927.

The author presents data of 27 blood sugar tests on 6 subjects who presented a subnormal blood sugar curve. He found that the administration of potassium iodide had no effect on the blood sugar curve, whereas thyroid medication caused a rise in all cases, persisting for at least a month after the thyroid medication had been stopped. Improvement followed the medication in 3 cases (50%) coincidentally with the rise of the blood sugar curve, or at a somewhat later period according to the author. The cases here studied

were: Myxoedema 1, bronchopneumonia 2, acute nephropathy 2, tonsillitis recidivans 1.—H. J. J.

Bone development in diabetic children. A Roentgen study. Morrison, L. B. and I. K. Bogan, Am. J. M. Sc. **174**: 313-319. 1927.

The authors made a study of 68 diabetics which were under 15 years of age. They found that the bone delevopment was in advance of the chronologic age with diabetes of recent onset, but with diabetes of long standing the bone development was below the chronologic age. Bone atrophy was observed in eight of the cases, but all of these children were less than eight and a half years old.
—E. L.

Absorption of insulin from the alimentary tract of depancreatized dogs, when protected by blood serum. Murlin, J. R. and Estelle E. Hawley, Am. J. Physiol. **83**: 147-161. 1927.

Observations on 5 depancreatized dogs proved beyond a doubt that insulin protected by blood serum from the proteolytic destruction of the digestive enzymes can be absorbed in significant amounts from the alimentary tract. In some instances the respiratory quotient was raised quite as high as following subcutaneous injection. In several instances the urine was made entirely sugar-free, although the dog was on full diet containing meat The effect on blood sugar was not so sudden or so great as when insulin is given subcutaneously. The liver seems to protect the body against the shock-like effects of a sudden access of insulin to the general circulation. Hypoglycemic shock was not seen following alimentary insulin even in huge doses. Four dogs have been kept alive, 81, 125, 41 and 91 days, respectively, after complete pancreatectomy and while on full diets. The dog which survived longest was pregnant, but lived 67 days after birth of the pups.—R. G. H.

The action of insulin on the respiratory metabolism of the isolated mammalian heart (L'azione della insulina sul ricambio respiratorrio del cuore isolato di mammifero). Peserico, E., Arch. di fisiol. **23**: 488-508. 1925.

Insulin increases the gaseous exchange and the respiratory metabolism of the normal isolated heart, and brings back to normal the low metabolism of the isolated diabetic heart. In both cases the amount of oxygen consumed and of carbon dioxide produced do not correspond to the total amount of glucose which disappears during the action of insulin. According to the author, insulin, instead of transforming the glucose into a more easily oxidizable form, is rather a direct activating element in preparing from the glucose the substances whose energy is used by the muscular fiber in the first phases of its contraction.—G. V.

Respiratory quotient curves in diagnosis in diabetes. Petty, O. H. and W. H. Stoner, Am. J. M. Sc. **171**: 842-846. 1926.

Twenty cases of normals, diabetic and renal glycosurics were studied by means of the glucose tolerance and basal metabolism tests. These authors found it necessary to make other tests besides the conventional glucose tolerance test for diagnosis. With the normals the respiratory quotient rose from the normal fasting level of 0.82-0.85 to 0.96, or 1, while with the diabetics the fasting respiratory quotients were 0.65-0.80 and rose but very little after the ingestion of the dextrose. Where renal glycosuria was present, the respiratory quotients were the same as in the normals. From their results the authors conclude that respiratory quotient studies made before and during the glucose tolerance test are a direct index of the sugar-burning ability of the individual. They also state that diabetes mellitus can be diagnosed earlier by this method than by a glucose tolerance test.—E. L.

Variations of phosphorus content in muscular tissue during insulin hypoglycemia (Le variazioni del contenuto in fosforo del tessuto muscolare durante l'ipoglicemia insulinica). Piazza, G., Arch. di farmacol. sper. **42**: 28-32. 1926.

Inorganic phosphorus (method of Bell and Doisy) and muscle sugar (Condorelli's method) were determined in small portions of rabbit muscle before and after injection of insulin. During insulin hypoglycemia there was neither augmentation of the organic phosphorus nor of the hydrolysable phosphorus portion.—P. M. N.

Insulin therapy in carcinoma (Tentativi di terapia insulinica nel carcinomatosi). Ponticaccia, L. and D. Campanacci, Giorn. di Clin. Med. **7**: 430-435. 1926.

Insulin hypoglycemia caused a slackening and an inhibition of development in experimental tumors. In six cancer cases insulin had good influence only on the weight, appetite and digestion.
—P. M. N.

Observations on the use of synthalin in the treatment of diabetes mellitus. Rabinowitch, I. M., Canad. M. A. J. **17**: 901-904, 1927.

Seven cases are reported. In the majority synthalin was effective, but in one or two non-effective, and in certain others a recurrence of glycosuria could not be cleared up by synthalin alone. It is noted that whenever a response to synthalin is obtained the resultant body-weight is less than that obtained on insulin balance, and it is suggested that the extra weight may be due to insulin oedema. Rabinowitch concludes that synthalin is effective in diabetes, but that on account of the variations found in results with it, it should only be at present employed where the metabolism of patients can be carefully observed.—A. T. C.

Sugar tolerance as an aid to diagnosis. Rowe, A. W., J. Am. M. Ass. **89**: 1403-1407. 1927.

An extensive series of sugar tolerance tests has been made with pure galactose. Healthy males were found to have a constant tolerance throughout life, but females, starting at a level below the male in the prepubertal years, exhibit a rising tolerance with sexual development and in maturity possess a level superior to that of the male. The menopause seemingly causes a retrogression toward the male level. Castration in the male does not produce any change; in the female, it causes a lowering which may reach the prepubertal level. Pregnancy lowers the mature tolerance, and menstruation seemingly shows a like tendency. Disturbed function of the several endocrine glands produces changes in the tolerance, the pituitary and the suprarenal exercising the greatest and the thyroid the least influence, if the testis is excluded. A variety of non-endocrine conditions, among which lesions of the central nervous system, syphilis, primary anemia, malignant tumors and liver diseases may be enumerated, tend to lower the tolerance, while serious renal disease may increase it.—R. G. H.

Further contribution to the study of the action of insulin on the ferments (Ulteriore contributo all'azione dell'insulina sui fermenti). Sammartino, U., Arch. di farmacol. sper. **42**: 17-27. 1926.

The author has experimentally demonstrated that in the reaction mixtures: diastase and starch; catalase and hydrogen peroxide; lipase and tributyrin, the addition of insulin does not modify the reaction velocities.—P. M. N.

Blood sugar content and insulin treatment of dermatoses. Simon, F., Arch. f. Verdauungskr. **37**: 363. 1926. Abst., J. Lab. & Clin. Med. **12**: 1121.

According to the author, a marked increase in blood-sugar value occurs in psoriasis and in furunculosis. In cases of psoriasis higher values are said to be noted in males than in females, while in furunculosis the increase is declared to vary within somewhat narrow limits. Blood-sugar value is said to exhibit an increase in the majority of cases of eczema, and to vary within wider limits. Highest values were encountered in relapses and in chronic cases, and relatively high values in eczema in diabetes mellitus. Insulin treatment of these dermatoses, which are accompanied by increase in blood sugar value, is declared to lead first to a temporary increase and later to a decrease in blood-sugar value. Thus, it is pointed out, pruritus is prevented and predisposition of the skin to injuries due to activity of bacteria is diminished. Simon is of the opinion that insulin may, through its increase in the alkalinity of the blood, exert a favorable effect upon many diseases of the skin.

The effect of insulin injected into the cerebrospinal fluid. Supniewski, J. V., Y. Ishikawa and E. M. K. Geiling, J. Biol. Chem. **74**: 241-246. 1927.

In three rabbits and six dogs insulin injected into the cerebellar cisterna caused only a slight decrease of sugar and phosphates in the blood, and in some cases an increase of these substances. Insulin incubated with fresh cerebrospinal fluid does not lose its hypoglycemic properties. Probably the explanation is that owing to the large size of the insulin molecule it passes from the cerebrospinal fluid into the circulation at an exceedingly low rate.—M. O. L.

The use of synthalin in diabetes (Zur synthalinbehandlung der Zuckerkranken). Umber, F., Deutsche med. Wehnschr. **7**: 27. 1927.

Synthalin is a derivative of guanidine, a nucleoprotein split product. The author treated 200 cases of diabetes with synthalin, which is supposed to lower the blood sugar and increase glycogen storage, but is not effective in coma. The article is illustrated with graphs. His patients responded by lowering and eliminating glycosuria, but most showed only a slight drop in blood sugar. There was never a normal glycemia in spite of a glycosuria. The best results were obtained from a combination therapy with insulin and synthalin. Non-diabetic glycosurias were as refractory to synthalin as to insulin. On synthalin therapy the weight increase was not like that with insulin; only three cases (of two hundred) gained from two to three kgm. The author also reports good results in children in combination therapy, insulin and synthalin. In surgical cases, insulin is the choice. The weak point in synthalin therapy is the toxic symptoms it produces. These appeared in 47% of the author's cases. (The average dose used was 25 mgm every other day for the adult.) The symptoms which appeared were: loss of appetite, malaise, headaches, sweating, oppressive feeling in stomach and pain, vomiting, diarrhea, and, in four vasomotor patients, tachycardia.—H. J. J.

Calcium studies in jaundice. With special reference to the effect of parathyroid extract on the distribution of calcium. Cantarow, A., S. M. Dodek and B. Gordon, Arch. Int. Med. **40**: 129-139. 1927.

The study was undertaken to compare the response to parathyroid extract in normal and in jaundiced persons. The series consists of fourteen cases of jaundice of various types and intensity. The blood clotting time, which was within normal limits in every case, was found to be reduced by parathyroid extract as in normal individuals, from 5.65 per cent, the maximum from 6-12 hours after the injection. The serum calcium values varied from 9.3 to 12 mgm. per 100 cc., slightly beyond normal limits, the response to parathyroid extract not being as marked as in normal persons. The

variations in the calcium content of whole blood was the striking feature of the study, the values ranging between 4.8 and 12 mgm. per 100 cc., bearing no relation to the coagulation time, degree, type or duration of the jaundice. This wide variation was the most marked difference observed between normal and jaundiced blood, the normal figures being 6.43-9.61 mgm. per 100 cc. Similar variations were observed in plasma calcium. The injection of parathyroid extract was followed by a marked decrease in the degree of variation. At the end of six hours, and particularly after twelve hours, the range in jaundiced patients was practically identical with that in normal individuals. The whole blood calcium level seemed to be independent of that of serum, two patients with identical serum values showing marked variation in whole blood calcium. The favorable effect of the hormone on the tendency of injured jaundiced tissue to bleed is due to the increased coagulability of the blood and to the diminished permeability of the capillary walls.
—Authors' Abst.

The rôle of toxins in parathyroid tetany. I. An attempt to control tetany by the oral administration of kaolin. Larson, E. and L. A. Elkourie, Am. J. Physiol. **83**: 231-236. 1927.

Kaolin given orally to 12 dogs did not have any decided effect in preventing or controlling tetania parathyreopriva. It was shown that kaolin does not adsorb guanidine in vitro from either an acid or alkaline medium. Guanidine was not adsorbed in significant amounts from either the ileum or the colon of an anesthetized dog during a period of one hour.—R. G. H.

Effect of parathyroid hormone on blood coagulability. (With special reference to jaundice). Zimmerman, L. M., Am. J. M. Sc. **174**: 379-388. 1927.

Due to the danger of post-operative bleeding from surgery in the presence of jaundice, this author studied the effect of parathyroid hormone on blood coagulation. The coagulation time in normal and icteric patients, as well as the calcium level of the blood, was determined before and after the injection of parathyroid hormone. There was no constant effect on the coagulation time after the administration of the parathyroid hormone. From his results the author concludes that increasing the calcium content of the blood does not diminish the coagulation time either in the presence or absence of jaundice.—E. L.

I. The effect of the parathyroid hormone on gastric secretion. II. The calcium content of gastric juice. Austin, W. C. and S. A. Matthews, Am. J. Physiol. **81**: 552-559. 1927.

The effect of parathyroid extract (parathormone) on the gastric response to histamine was studied in four dogs with Pavlow

pouches. It was found that if the parathyroid hormone influence is severe and prolonged, and the water balance of the body is unfavorable because of restricted intake and increased elimination of water, the gastric response of the dog to histamine may be decreased. If the parathyroid hormone is administered in large amounts, and the water balance of the body more favorably maintained, the gastric response of the dog to histamine is normal. After overdosage of the dog with parathyroid hormone, the Pavlow pounch continues to secrete until the beginning of hemorrhage, when it stops completely and suddenly. The calcium content of pure gastric juice of the normal dog is 5 to 6.5 mgm. in 100 cc. The calcium content of gastric juice of the dog is not greatly influenced by administration of the parathyroid hormone in amounts sufficient to elevate the blood calcium to the level of 18 or 19 mgm. in 100 cc.—R. G. H.

Parathyroid in the treatment of tropical sprue.—Baumgartner, E. A., Am. J. Trop. Dis. [etc.], **7**: 381-391. 1927.

Three quite severe cases of tropical sprue are described in some detail. All of these cases had low blood calcium and definite evidences of tetany and the effect of parathyroid extract on them is studied by noting the blood calcium changes. The first case entered with well marked signs of tetany, her blood calcium was 6.2 mgms. per 100 cc. blood. Following the administration of 5 cc. of Collip's parathyroid extract there was a definite rise of blood calcium to 8.1, which fell again and was not raised by a second series of injections of 4 cc. of parathyroid preceded by a blood transfusion. A third series was again effectual in causing an increased blood calcium. Thereafter the dry extract of parathyroid was used, 1/10 grain thrice daily for a month and then at intervals of a few days. The second case was given the dry extract daily over a period of four months, although she entered with a normal blood calcium and with no sign of tetany. At the end of two months the blood calcium decreased. Six weeks later signs of tetany were present. The patient left the author's charge, continued for some months, then developed definite tetany spasms and died. A third case with a very low blood calcium improved markedly on the dry extract with calcium lactate. It is believed the dry extract can help raise blood calcium, that if given over a long period it may help deplete the tissue reserve calcium.—Author's Abst.

Parathyroid preservation. Terry, W. I. and H. H. Searls, J. Am. M. Ass. **89**: 966-967. 1927.

In the standard operation of partial thyroidectomy, a surprisingly large number of parathyroid glands are being removed as a result of their frequent relationship to the anterior and lateral capsule of the thyroid gland. Their removal or injury is very frequently followed by moderate transient evidence of parathyroid

deficiency. By careful inspection, these bodies may often be identified and preserved. Routine preservation of the lateral capsule is an additional safeguard which should be adopted as a simple modification of present technic. Even though the symptoms of this deficiency are transient and followed practically always by complete recovery, it will be conceded that parathyroid tissue is of extreme value to the patient and should not be removed or injured.
—Author's Abst.

Parathyroid hormone and the calcification of fracture callus. Lehman, E. P. and W. H. Cole, J. Am. M. Ass. **89**: 587-588. 1927.

In 13 to 14 white rats, the injection of parathyroid extract did not hasten the calcification of fracture callus, as judged by breaking strength. In fact, the breaking strength of the callus of the treated rats was slightly less than that of the controls.—R. G. H.

Tumors of the pineal gland. Haldeman, K. O., Arch. Neurol. & Psychiat. **18**: 724-754. 1927.

Two cases of glioma of the pineal gland are reported with complete clinical and pathologic characteristics. In view of the contradictory results obtained in the experimental work on pineal gland feeding of animals and of defective children and on the destruction of the pineal gland in animals, it is impossible to draw any conclusions regarding the function and significance of this gland. A tumor of the pineal gland in a child is occasionally accompanied by precocious sexual development and adiposity or general overgrowth, which with symptoms of internal hydrocephalus make up the syndrome designated by Pellizzi as "macrogenitosomia praecox." One hundred and thirteen cases of tumor of the pineal gland are summarized in chronological order. Tabulation of the microscopic picture presented in the 113 cases shows: sarcoma, 24 cases; teratoma, 22 cases; cyst, 14 cases; glioma, 11 cases; pinealoma, 10 cases; hyperplasia, 4 cases; carcinoma, 4 cases; adenoma, 4 cases, psammoma, 2 cases, and unclassified, 18 cases. The syndrome of "macrogenitosomia praecox" was observed in 16 cases of pineal tumor, all in males between the ages of 3 and 16 years. Blindness or impairment of vision occurred in 45 cases, or in more than one-third of the total. The most important of the eye signs in cases of pineal tumor are paralysis of upward movement, diplopia, abducens paralysis, nystagmus, ptosis, and absence of the pupillary light reflex. Of the 102 cases in which the sex was reported, 78 occurred in males and 24 in females. The incidence was greatest during the second decade (29 cases), although 28 patients were reported between 21 and 30 years of age, and 24 under 11 years. No conclusion can be drawn from the two cases of hypoplasia or absence of the pineal gland. A bibliography of 157 citations is appended.—Author's Abst.

Effects of prolonged administration of desiccated spleen and red bone marrow on the blood forming centers of rabbits. Leake, C. D., J. Pharmacol. & Exper. Therap. **31**: 216. 1927.

One group of rabbits were bled daily for 15 days; a second received 1 gm. desiccated spleen and bone marrow in equal weight for the same period; the third group served as controls. At the end of this period, the first group showed extensive hyperplasia of the bone marrow with a red count below 2,000,000. The second group showed moderate marrow hyperplasia and a red count above 6,000,000. The control group showed normal fatty bone marrow and a count ranging between 5,000,000 and 6,000,000.—C. I. R.

On three cases of thymus death of infants. Takashima, T., Journal of Hokuetsu Medical Society, **41**: (4 and 6). 1926. Abst., Japan Medical World, **7**, 147.

The author reports the pathologico-anatomical findings in three cases of thymic death—a 27-day-old boy, a 2 months old boy and a 9 months old boy. All these three died while sleeping without the least noticeable changes during sleep by their parents. At autopsy they were all found to have had hypertrophy of the thymus, especially of the cortical layer of the organ, and had specific thymic endocrine intoxication features.

A comparison of the action of natural and synthetic thyroxin (Vergleichende Untersuchung der Wirkung von aus Schilddrüsen gewonnenem Thyroxin und von synthetisch bereitetem). Abderhalden, E. and J. Hartmann, Arch. f. d. ges. Physiol. **217**: 531-534. 1927.

Natural and synthetic thyroxin produce the same action on the growth and metamorphosis of tadpoles.—A. T. C.

The relation of thyroxin action to the sympathetic nervous system (Beziehungen der Thyroxinwirkung zum sympathischen Nervensystem). Abderhalden, E. and E. Wertheimer, Arch. f. d. ges. Physiol. **216**: 697-711. 1927.

Thyroxin produces its action through the sympathetic. When action through the sympathetic is inhibited by ergotamine, thyroxin no longer produces action on metabolism.—A. T. C.

Langhans' proliferating goiter. Bircher E., Beitr. z. klin. Chir. **139**: 383. 1927. Abst., J. Am. M. Ass. **89**: 1288.

In the past twelve years, Bircher has seen thirty-six cases of Langhans' proliferating goiter (adenocarcinoma, according to Eiselsberg and Erdheim). He did not find it to be malignant clinically, but it has certain characteristics that separate it from the main goitre group. It has a strong predilection for childhood, and it is

refractory to iodine. Insufficiency of the pulmonary circulation, with weakening of the power of the heart from dyspnea caused by compression of the trachea, was frequent. Both hyperthyroid and hypothyroid phenomena were seen. The tendency to recur is strong and is manifested early.

Control of hyperthyroidism by thyroidectomy. Elliott, C. A., J. Am. M. Ass. **89**: 519-522. 1927.

The status of 100 patients from six months to six years after thyroidectomy performed for the relief of hyperthyroidism, is as follows: Seventy consider themselves perfectly well; thirty are conscious of some disability; all are carrying on their usual work. Forty-one show evidence of definite visceral injury as the result of previous hyperthyroidism. Of 14 cases of exophthalmic goiter in which operations were performed within 3 months of the onset of symptoms, only one shows residual visceral damage. Four patients are considered to have persisting but not disabling hyperthyroidism insufficient to require operation. Five patients are definitely hypothyroid, and are benefited by thyroid extract. Laryngeal nerve injury occurred temporarily in 6 cases; in 2 the injury has persisted. Reoperation for thyroid remnants was necessary in 6 cases.

—Author's Abst.

The rôle of thyroid and parathyroid glands in growth of heart and lungs. Hammett, F. S., Am. J. Anat. **39**: 219-238. 1927.

A report and interpretation has been made of the growth responses of the heart and lungs to thyroid and parathyroid deficiencies initiated at different ages during the period of active post-natal growth of the albino rat. A general growth retardation is produced. This is due to the dependency of the heart and lungs on the effectiveness of the growth of the body as a whole, the which is lowered under the experimental conditions. Hence the conclusion is that the growth of these organs is not specifically related to either thyroid or parathyroid function. The increment of gonadal incretory activity which occurs at puberty exerts its characteristic influence on the response to the glandular deficiencies.

—Author's Abst.

The rôle of thyroid apparatus in the growth of liver, kidneys and spleen. Hammett, F. S., Am. J. Anat. **39**: 239-266. 1927.

A report and interpretation has been made of the growth response of the liver, kidneys and spleen of male and female albino rats to thyroid and parathyroid deficiencies initiated at successive stages of development during post-natal growth. There is no evidence that the growth of the liver, kidneys or spleen is specifically related to thyroid activity. The growth retardation which occurs is attributable to the relation of the type of metabolism characteristic

of the individual organ, to the retardation in effectiveness of the growth processes of the body as a whole, resulting from the lowering of the metabolic rate on the thyroid removal. The increment of gonadal incretory activity which takes place at the pubertal adjustment so acts on the metabolic substrate of the three organs that their sensitivity to the general effects of thyroid deficiency is greatly enhanced, and weight is lost instead of gained. There is no evidence that parathyroid activity has any specific relation to the growth of the liver or kidneys. The data show that the toxemia of parathyroid deficiency has a specific influence on spleen weight. It is probable that this is an expression of an influence on spleen volume exerted through the autonomic nervous system, rather than of an influence on spleen growth as such. Puberty exerts its characteristic influence in accentuating the sensitivity of these organs to parathyroid removal.—Author's Abst.

Studies of the thyroid apparatus. L. Interpretative generalizations from the differential development observed in conditions of thyroid and parathyroid deficiency. Hammett, F. S., Am. J. Physiol. **82**: 250-260. 1927.

From an analysis of a very extensive body of original data, Hammett concludes that distortion of differential development follows both thyroid and parathyroid removal. With the exception of the hypophysis, the submaxillaries, and possibly the spleen, this is not due to any specific relation of glandular functions to organ growth, but to the general metabolic disturbance induced by the deficiencies. The growth of some organs is more resistant and that of others is more sensitive than that of the body as a whole. The basis of this differential reaction lies in the relation of the metabolic processes of the organs in question to the bodily economy as a whole. The distortion is consistent in direction and produces a distinctly modified type of structural organization. The broader aspects of this finding are referred to in their relation to evolutionary development.—R. G. H.

Studies on Metabolism. VI. Experimental hyperthyroidism. Kunde, Margaret M., Am. J. Physiol. **82**: 195-215. 1927.

Extended experiments were carried out on seven dogs. It was found that no significant change occurs in the basal metabolism for 7 to 12 hours after the administration of a single dose of Kendall's thyroxin (intravenously) or desiccated thyroids (orally). Following this, an appreciable increase in the heat production occurs, which is most marked on the second day. After daily repeated doses of either desiccated thyroids or Kendall's thyroxin, the basal metabolism progressively increases, reaching a maximal three weeks or more after administering the initial dose. The maximal increase in the heat production resulting from experimental hyper-

thyroidism is 120% above normal in the dog with intact thyroid glands and 170% above normal in the previously thyroidectomized animal. This rise in metabolism is always accompanied by fever. Tachycardia and a disturbance in the conductive mechanism of the heart may both occur as a result of induced hyperthyroidism in the dog. The influence on the body weight of experimental hyperthyroidism depends entirely on an undetermined nutritional state. Some dogs display a peculiar ability to retain a constant body weight during several weeks of advanced hyperthyroidism on a previously determined maintenance diet. Others may lose 35% of their initial body weight. Diarrhoea, tenesmus and bloody stools may occur as a result of hyperthyroidism. Severe skin lesions of an eczematous character may occur in some dogs during the crisis of hyperthyroidism. Exophthalmos cannot be demonstrated in the dog, but in the rabbit the administration of thyroid substance results in a pronounced exophthalmos, provided the rabbit has previously been in a myxedematous condition, due to thyroidectomy. Hyperglycemia and glycosuria do not occur in the dog during experimental hyperthyroidism. The pathological changes in the thyroid gland during advanced hyperthyroidism consists essentially in a generalized disintegration of the gland with elongated follicular cells containing oval nuclei, and fibroblastic in appearance. Iodine injected intravenously in the form of potassium iodide does not reduce the basal metabolism of normal dogs. In the dog iodine in the form of Lugol's solution is ineffective in reducing the high basal metabolism or in preventing the metabolism from increasing during the ingestion of thyroid substances. Our results fail to support the theory that some of the clinical symptoms of either hyperthyroidism or exophthalmos are due to a perverted secretion, since all of the cardinal symptoms of a disturbance in the functional activity of the thyroid gland, excepting cretinism and myxedema, can be produced in either the dog or the rabbit under certain conditions, by the administration of thyroid substances obtained from the glands of normal animals. A quantitative relationship between the amount of thyroid substance ingested and the increase in the basal metabolism does not exist, neither is the catalytic theory of Plummer and Boothby adequate for explaining the results of the present experiments on hyperthyroidism. The degree of toxicity resulting from the ingestion of a given amount of thyroid substance varies markedly with different animals of the same species and depends on some condition of the cells, which at present seems closely related to water metabolism and dehydration phenomena. The thyroidectomized dog and rabbit are more susceptible to the ingestion of thyroid substances than animals with thyroid glands intact. In a thyro-parathyroidectomized dog, in a tetanoid state, the administration of thyroid substances exerted a marked influence on the control of parathyroid tetany.

—Author's Summary.

Experimental cretinism. I. A rachitic-like disturbance in extreme hypothyroidism. Kunde, M. M. and A. J. Carlson, Am. J. Physiol. **82**: 630-638. 1927.

A study was made of 404 thyroidectomized rabbits shown by their weight curves to be actually hypothyroid. It was found that cretin rabbits (thyroidectomized between 2 and 3 weeks after birth) develop a condition of disturbance in skeletal development which fundamentally stimulates clinical rickets. This is not due to a dietary deficiency. This rickets-like condition is accompanied by severe anemia. It is characterized by a normal or slightly depressed concentration of the blood calcium and a low acid soluble phosphorus of the serum.—R. G. H.

Experimental cretinism. II. The influence of the thyroid glands on the production and control of experimental rickets. Kunde, M. M. and L. A. Williams, Am. J. Physiol. **83**: 245-249. 1927.

Experiments were made upon 46 rats. It was found that no amount of cod liver oil added to a ricket-producing diet is adequate to prevent the development of rickets in cretin rats as determined from histological studies of the epiphysis. Supplying antirachitic vitamines in the form of vitamine-rich foodstuffs to a nutritious diet consisting of table scraps failed to prevent the occurrence of rickets.

—R. G. H.

Thyroid gland substance implantations. Kurtzman, H. and H. Hubener, Zentralbl. f. d. ges. Med. **54**: 1666. 1927.

This article reviews in brief the various methods of transplanting thyroid gland. All of these methods had negative results as to the continued growth and functioning of the gland. The substance was, after a period of time, absorbed and scar tissue formed. The authors have treated three myxoedematous cretins by thyroid gland substance implantations. The thyroid gland was scraped and the substance injected subcutaneously into the cretins by means of a pressure syringe. In one case the subject, aged 11, showed improvement after the treatment with a mental awakening. The second subject, age 13, showed no improvement at all. The third child, with a mental age of two and a half years and with osseous maldevelopment, could utter only unintelligible sounds. After three injections over a period of one year the child tried to repeat spoken words, was livelier and became more active mentally. The authors conclude that the resulting effects were by no means over-estimated, but furnish proof that mental and physical improvement may be obtained by injection of thyroid tissue in myxoedematous cretins.

—L. L. Stanley.

Adiposity of pituitary and thyro-pituitary origin in the adult: its diagnosis and treatment. Masterman-Wood, J. L., Practitioner, **119**: 165-172. 1927.

Four cases are briefly presented.—J. C. D.

Exophthalmic goiter and diabetes (Ein Kombinationsfall von Jodbasedow und Diabetes [Zugleich ein Beitrag zu den insulin-refraktäsen Diabetesfällen]). Orator, V., Deutsche Ztschr. f. Chir. **201**: 402-406. 1927.

The author reports a case of a man, 47, who nine years previously was afflicted with arthritides and rheumatism, at which time he developed glycosuria, which promptly subsided on diet. In 1927 he was treated for atherosclerosis with Sajodin, and out of his symptomless enlarged goiter he developed hyperthyroidism—also symptoms of diabetes, glycosuria 1%, which insulin (20 units 2 to 3 times per day) did not wholly control. Following thyroidectomy, the glycosuria cleared up without any more insulin, and the patient was discharged as cured of both diabetes and hyperthyroidism.

—H J. J.

Radiation therapy in malignant diseases of the thyroid gland. Portmann, U. V., J. Am. M. Ass. **89**: 1131-1135. 1927.

Of 166 patients treated or untreated, 28.3% are living more than one year, and 24, or 14.4%, more than three years since they first came under observation. Among the 125 patients who could be treated, 37.6% are living more than one year, 24, or 18.8%, more than three years, and 12.8% for five or more years after treatment was instituted. Apparently the best results are obtained by operation followed by irradiation, for in this group 22.6% of the patients are "five-year cures"; while 20, or 36.6%, are living more than three years after treatment. If this plan of treatment is followed in all cases, radiation will be applied in some cases, in which the tumors are small, localized and encapsulated, and might therefore be cured by surgery alone; nevertheless, the final results indicate the advisability of applying radiation in every case of malignant disease of the thyroid gland. The explanation for this observation may lie in the fact that apparently the cellular structures of many malignant growths of the thyroid are sensitive to radiation because of their fetal or embryonic origin, and because metastasis must take place through small blood vessels or lymphatics, which are also comparatively susceptible to radiation. In the author's experience, treatment of thyroid diseases with radium has been somewhat less satisfactory than with roentgen rays on account of a tracheitis which has occurred in almost all cases. It is deemed necessary in each case to treat the upper mediastinum as well as the gland area, and this is practically impossible with radium. In treating malig-

nant disease, it is important to prevent the occurrence of malignant disease, if possible. About 2% of all thyroid cases presented malignant disease, and since 90% of the malignant conditions of the thyroid gland originate in fetal adenomas, the author believes that all adenomas of the thyroid should be removed as a prophylactic measure. This is especially true in later life, during the years when a malignant condition most frequently develops. Prevention is more important than treatment.—R. G. H.

The iodine content of the thyroid gland of various types of cattle and its relation to the glandular condition. Von Fellenberg, T. and H. Pacher, Mitt. a. d. Geb. d. Lebensmittelunt. u. Hyg. **18**: 265-289. 1927. Abst., Chem. Absts. **21**: 3941.

Analysis of 80 different thyroid glands shows little relation between the iodine content and other conditions of the gland. The iodine content generally was not dependent upon the size. In certain bovine species, it varied inversely to the gland size. The absolute iodine content increased with the weight of the gland. A low iodine value accompanied a low content of colloidal matter and small follicles. Single species showed different thyroid weights and contents, so that external conditions as environment, climate, iodine, food, etc., may have more effect than actual glandular condition.

The action of iodine preparations on the metamorphosis of axolotls (Ueber die Wirkung der Jodpräparate auf die Metamorphose der Axolotl). Zawadovsky, B., A. A. Titajev, Z. M. Perelmutter and N. A. Raspopowa. Arch. f. d. ges. Physiol. **217**: 198-203. 1927.

Thyroxin in single injection of 0.01 mgm. produces complete metamorphosis of Axolotls of 10 grams average weight. Tyrosine and tryptophane given with simultaneous iodine injection, and di-iodotyrosine and di-iodotryptophane in doses up to 30 mgm. do not produce this complete metamorphosis. The latter compounds cannot be compared with thyroxin, and can only serve as material for thyroxin production in the thyroids of the animals tested.

—A. T. C.